SEP 25 2008
PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

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| In re application of | : | **Confirmation No. 1112** |
| Edwin SOUTHERN | : | Attorney Docket No. 2004_0200 |
| Serial No. 10/772,467 | : | Group Art Unit 1631 |
| Filed February 6, 2004 | : | Examiner Anna Skibinsky |
| ANALYZING POLYNUCLEOTIDE SEQUENCES | : | **Mail Stop: Appeal Brief- Patents** |

## APPEAL BRIEF UNDER 37 CFR §41.37

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is responsive to the Notice of Appeal dated February 25, 2008, the time for responding thereto being extended for five months in accordance with a petition for extension submitted concurrently herewith. The following is appellant's Appeal Brief, submitted under the provisions of 37 CFR § 41.37. Pursuant to the provisions of 37 CFR § 41.20, this brief is submitted with a fee of $510.00.

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## I. <u>REAL PARTY IN INTEREST</u>

A statement identifying the real party in interest.

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The real party in interest is Oxford Gene Technology Limited.

## II. RELATED APPEALS AND INTERFERENCES

A statement identifying by application, patent, appeal or interference number all other prior and pending appeals, interferences or judicial proceedings known to appellant, the appellant's legal representative, or assignee which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal. Copies of any decisions rendered by a court or the Board in any proceeding identified under this paragraph must be included in an appendix as required by paragraph (c)(1)(x) of this section.

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This application is a divisional of S.N. 09/422,803 filed October 22, 1999, now abandoned, which is a divisional of S.N. 08/925,676 filed September 9, 1997, now issued as U.S. Patent No. 6,054,270, which is a divisional of S.N. 08/230,012 filed April 19, 1994, now issued as U.S. Patent No. 5,700,637, which is a continuation of S.N. 07/695,682 filed May 3, 1991, now abandoned, which is a continuation-in-part of S.N. 07/575,317 filed September 28, 1990, now abandoned, which is a U.S. national stage of International Application No. PCT/GB89/00460 filed May 2, 1989, which claims priority upon Great Britain patent application S.N. 8810400.5 filed May 3, 1988.

There are no prior or pending appeals or interferences which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

There have been various judicial proceedings concerning infringement of U.S. Patent Nos. 5,700,637 and 6,054,270. There was no court decision which adversely affected the validity or enforceability of the patents. Several court proceedings might be viewed to be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal. The proceedings are the following:

(1) Oxford Gene Technology Ltd. v. Affymetrix, Inc., Civil Action No. 99-348-JJF before the United States District Court for the District of Delaware (Infringement Action based upon U.S. Patent No. 5,700,637).

(2) Oxford Gene Technology Ltd. v. Mergen Ltd., et al., Civil Action No. 02-1695-KAJ before the United States District Court for the District of Delaware (Infringement Action based upon U.S. Patent No. 6,054,270).

(3) Oxford Gene Technology Ltd. v. Motorola, Inc., Civil Action No. 02-9344 before the United States District Court for the Northeastern District of Illinois (Infringement Action based upon U.S.Patent No. 6,054,270).

(4) Oxford Gene Technology Ltd. v. Telechem International, Civil Action No. 04-0013 before the United States District Court for the District of Delaware (Infringement Action based upon U.S. Patent No. 6,054,270).

(5) Oxford Gene Technology Ltd. v. Nanogen Inc., Civil Action No. 02-1687 before the United States District Court for the District of Delaware (Infringement Action based upon U.S. Patent No. 6,054,270).

There are pending reexamination proceedings concerning claims of U.S. Patent Nos. 5,700,637 and 6,054,270. U.S. Patent No. 5,700,637 is subject to reexamination in Control Nos. 90/008,429 and 90/008,844. U.S. Patent No. 6,054,270 is subject to reexamination in Control Nos. 90/008,428, 90/008,830 and 90/010,020. No final decision has been reached in these proceedings.

## III. STATUS OF CLAIMS

A statement of the status of all the claims in the proceeding (e.g., rejected, allowed or confirmed, withdrawn, objected to, canceled) and an identification of those claims that are now being appealed.

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Claims 17-36 and 86-89 are pending. Claims 1-16 and 37-85 are canceled. Claims 17-27 and 86-87 are rejected. Claims 28-36 and 88-89 are withdrawn. The rejection of claims 17-27 and 86-87 is appealed.

## IV. STATUS OF AMENDMENTS

A statement of the status of any amendment filed subsequent to final rejection.

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An amendment was filed on November 20, 2007 subsequent to the final Office Action of August 23, 2007. The amendment was denied entry in the Advisory Action of December 21, 2007.

## V. SUMMARY OF CLAIMED SUBJECT MATTER

A concise explanation of the subject matter defined in each of the independent claims involved in the appeal, which shall refer to the specification by page and line number, and to the drawing, if any, by reference characters. For each independent claim involved in the appeal and for each dependent claim argued separately under the provisions of paragraph (c)(1)(vii) of this section, every means plus function and step plus function as permitted by 35 U.S.C. 112, sixth paragraph, must be identified and the structure, material, or acts described in the specification as corresponding to each claimed function must be set forth with reference to the specification by page and line number, and to the drawing, if any, by reference characters.

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Claims 17 and 86 are the only independent claims under appeal. No claim involved in the appeal recites means plus function or step plus function features.

Claims 17 and 86 are each directed to an apparatus for analysing a polynucleotide. The claimed invention is in the field that has become known as "DNA arrays" or "gene chips".

The apparatus of claim 17 comprises a support having an impermeable surface. See page 1, lines 24-25 and page 10, line 22 of the substitute specification filed on August 16, 2004. Hereinafter all references to the specification will relate to the substitute specification. Attached to this surface is porous material. See page 11, lines 1 and 8. Attached in turn to the porous material is an array of oligonucleotides with predetermined sequences, wherein the array comprises at least two defined cells, and the sequence of the first oligonucleotides of a first cell is different from the sequence of the oligonucleotides of the second cell. See page 1, line 24 to page 3, line 16; page 7, line 11 to page 8, line 24; page 10, line 13 to page 11, line 12; and page 16, line 21 to page 17, line 6. The oligonucleotides are shorter than the polynucleotide. See page 12, lines 17-22.

The apparatus of claim 86 has the same requirements as the apparatus of claim 17, with the further requirement that the oligonucleotides are covalently attached to the porous material. See page 11, lines 16-18.

During use, a polynucleotide sample is contacted with the apparatus under hybridising conditions such that base pairs can form between the sample's polynucleotides and the immobilized oligonucleotides. Thus polynucleotides within the sample will be retained within cells of the

array where the sequences are complementary and can form a duplex. If the polynucleotides are labeled, then cells where hybridisation has occurred can easily be visualized. Because the sequences of the immobilized oligonucleotides in these cells are predetermined, it is then a simple task to confirm that the sample contains the corresponding sequence. Conversely, it is also possible to confirm that the sample does not contain sequences that correspond to cells where label was not retained.

For instance, a sample might contain fluorescently-labelled mRNA prepared from human cells, indicating their gene expression profile. If a researcher has 1000 genes of interest they can design DNA oligonucleotide probes specific for each of them. These oligonucleotides can be attached to a porous material within an apparatus of the invention to form cells of the array. Thus the apparatus might contain an array of 1000 cells, each with a different oligonucleotide specific for a different gene. The sample can then be incubated with the apparatus under hybridising conditions such that the mRNA molecules can hybridize to the immobilized DNA oligonucleotides. After hybridization, the researcher can see which of the 1000 cells contain fluorescent signals and thus can determine which of the 1000 genes were being expressed in the original human cells.

The porous material in the apparatus can be microporous (claim 18) and may be made of a silicon oxide such as glass (claims 19 & 20). Although arrays with only a few cells are useful it is typical for them to include at least 72 cells (claim 21). Each cell will typically include at least $3 \times 10^{-12}$ µmol[1] of oligonucleotides (claim 22).

In preferred apparatuses, the oligonucleotides are attached to the porous material by covalent bonds (claims 23 and 86) and this is more preferably via one of the oligonucleotide's terminal residues (claims 24 and 87).

The oligonucleotides may be prepared externally and then attached to the porous material, but a useful way of making them is to synthesize them *in situ* within the apparatus (claim 25).

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[1] A typographical error has been discovered in claim 22, in that "mmol" should read "µmol". See page 12, line 11.

The oligonucleotides may be applied to the apparatus by using a computer-controlled device (claim 26) such as a computer-controlled printing device (claim 27). For example an inkjet printer can be used to deliver pre-synthesized oligonucleotides onto the apparatus for attachment, or can be used to deliver nucleotide precursors during *in situ* synthesis of the oligonucleotides. See page 10, line 13 to page 11, line 5; page 19, line 20 to page 20, line 9; and page 24, line 16 to page 25, line 12.

## VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A concise statement of each ground of rejection presented for review.

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There is a single ground of rejection presented for review. Claims 17-27 and 86-87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stavrianopoulos et al. (U.S. Patent No. 4,994,373) in view of Matkovich et al. (U.S. Patent No. 4,828,386).

## VII. ARGUMENT

The contentions of appellant with respect to each ground of rejection presented for review in paragraph (c)(1)(vi) of this section, and the basis therefor, with citations of the statutes, regulations, authorities, and parts of the record relied on. Any arguments or authorities not included in the brief or a reply brief filed pursuant to §41.41 will be refused consideration by the Board, unless good cause is shown. Each ground of rejection must be treated under a separate heading. For each ground of rejection applying to two or more claims, the claims may be argued separately or as a group. When multiple claims subject to the same ground of rejection are argued as a group by appellant, the Board may select a single claim from the group of claims that are argued together to decide the appeal with respect to the group of claims as to the ground of rejection on the basis of the selected claim alone. Notwithstanding any other provision of this paragraph, the failure of appellant to separately argue claims which appellant has grouped together shall constitute a waiver of any argument that the Board must consider the patentability of any grouped claim separately. Any claim argued separately should be placed under a subheading identifying the claim by number. Claims argued as a group should be placed under a subheading identifying the claims by number. A statement which merely points out what a claim recites will not be considered an argument for separate patentability of the claim.

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Claims 17-27 and 86-87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stavrianopoulos et al. (U.S. Patent No. 4,994,373) in view of Matkovich et al. (U.S. Patent No. 4,828,386).

*Claims 17 to 22 and 26 to 27*

A. Stavrianopoulos and Matkovich Are Not Analogous Art

To rely on a reference under 35 U.S.C. 103, it must be analogous art. M.P.E.P. 2141.01(a). Stavrianopoulos and Matkovich are not analogous art, and one skilled in the art would not have looked to Matkovich to modify the invention of Stavrianopoulos. A copy of Stavrianopoulos and Matkovich are attached in the Evidence Appendix.

Stavrianopoulos deals with nucleic acid assays, whereas Matkovich is explicitly concerned with antibody assays (*e.g.* see the Background section of Matkovich, culminating with the statement: "*Accordingly, there remains a need for improvements in multiwell plates to provide for increased antibody binding in a more reliable manner*". In addition, the Summary of the Invention section refers specifically to surfaces "*capable of binding antibody*", etc.). A skilled person starting with the DNA assay of Stavrianopoulos would not obviously have looked to the

teachings of Matkovich because it is from a different technical field (antibodies *vs.* nucleic acids); rather, they would have looked within their own field (nucleic acid assays).

Even if the skilled person had turned to the antibody field, they would not have modified the Stavrianopoulos apparatus in the manner suggested by the examiner. The examiner writes that a *"person of ordinary skill in the art would be motivated to use the porous membrane on top of the impermeable surface of Stavrianopoulos et al. because Matkovich et al. teach that a porous surface results in a better binding capacity of biological substances"* (see the final Office Action dated August 23, 2007, page 6, section 13). However, this apparent motivation runs contrary to the explicit teachings of Stavrianopoulos. At column 5, lines 46-52, Stavrianopoulos concludes that porous support materials are *"less desirable for practice of the method of the present invention"*. It is not reasonable to think that the skilled person would ignore this clear discouragement. Stavrianopoulos is teaching away from the attachment of nucleic acids to porous materials, and so is teaching away from the claimed apparatus and from the surface modifications disclosed in Matkovich.

> "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re ICON Health and Fitness, Inc.*, 496 F.3d 1374, 1381, 83 U.S.P.Q.2d 1746, 1751 (Fed. Cir. 2007), citing *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994); and *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007) at 1739–40 (explaining that when the prior art teaches away from a combination, that combination is more likely to be nonobvious).

Overall, therefore, the examiner's rejection of claim 17 requires a skilled person starting with Stavrianopoulos to look to an unrelated technical field for a disclosure that contradicts the clear preferences of the starting point. A person of ordinary skill would not have made these choices, and it is only with hindsight that they seem reasonable.

"One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir.1988).

"It is impermissible . . . simply to engage in a hindsight reconstruction of the claimed invention, using the applicant's [invention] . . . as a template and selecting elements from references to fill the gaps." *In re Gorman*, 933 F.2d 982, 987, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991).

As stated in *In re Fritch*, 972 F.2d 1260, 1266, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992): "It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious. This court has previously stated that '[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention' (citations omitted)".

B. Stavrianopoulos Fails to Teach or Suggest "an array of oligonucleotides with predetermined sequences" according to Claim 17

Claim 17 requires the apparatus to include *"an array of oligonucleotides with predetermined sequences"*. The term "predetermined sequences" was considered during examination of earlier applications in the same family, including the application that was issued as U.S. Patent No. 5,700,637. The reasons for allowance in U.S. Patent No. 6,054,270 dated November 30, 1999 noted that *"the phrase 'predetermined sequences' ... is interpreted to require that the complete sequence of each and every oligonucleotide probe on the array surface is known ... "*. The appellant accepted this interpretation at the time and has never adopted a different interpretation for any continuing or divisional applications derived from U.S. Patent No. 5,700,637 (including the present application).

Thus the *"array of oligonucleotides with predetermined sequences"* in the apparatus of claim 17 is an array in which the sequence of each immobilized oligonucleotide is known. In contrast, the immobilized sequences in Stavrianopoulos are unknown. This is a fundamental distinction

between the Stavrianopoulos and the present claims. The apparatus that is made and used in the Stavrianopoulos assay contains an immobilized analyte to which free probes are then hybridized (see column 5, lines 37-60: *"Analytes in a biological sample are preferably denatured into single-stranded form, and then directly fixed to a suitable solid support ... Chemically-labeled probes are then brought into contact with the fixed single-stranded analytes under hybridizing conditions."*) The analyte is a DNA or RNA molecule about which information is sought (see column 1, lines 28*ff*) and so the immobilized nucleic acids do not have *"predetermined sequences"*. In contrast to the immobilization of analytes in Stavrianopoulos, the presently-claimed apparatus uses immobilized *"oligonucleotides with predetermined sequences"* and analytes are then hybridized to these immobilized oligonucleotides. Thus Stavrianopoulos is a "mirror image" of the present claims, in which known and unknown are reversed.

Nothing in Matkovich suggests that the analyte and probe should be reversed and so a combination of Stavrianopoulos and Matkovich would not lead to the present apparatus.

The examiner takes the position that Stavrianopoulos teaches an array comprising predetermined sequences, for example, DNA from specific samples such as lambda DNA (column 9, lines 25-41) or adenovirus (column 11, line 21). See sections 4 and 16 of the final Office Action.

However Stavrianopoulos clearly teaches that these specific samples are analytes immobilized on the support, to which glucosylated DNA labeled probes are contacted. It is clear that the purpose of such constructs is to determine whether the immobilized samples contain the sequences of the labeled probes. Thus the immobilized sequences of Stavrianopoulos are not known or predetermined as required by claim 17. Nor is there any teaching or suggestion in Stavrianopoulos that the sequences of the immobilized sequences are known.

The examiner takes the position that the specification does not provide a specific definition of the term "predetermined" sequence to be a "known sequence". However there is no requirement that claim terms be specifically defined in a patent specification. According to PTO practice, the words of a claim must be given their plain meaning, unless the plain meaning is inconsistent with the specification. M.P.E.P. 2111.01(I). The ordinary and customary meaning of a term may be

evidenced by a variety of sources, including the words of the claims themselves, the remainder of the specification, the prosecution history, etc. M.P.E.P. 2111.01(II).

One skilled in the art reading the instant specification would clearly understand that the complete sequences of the immobilized oligonucleotides are known. The immobilized oligonucleotides are contacted with labeled analytes. The sequence of the oligonucleotides to which the labeled analytes are bound is known based upon a "look up table". See page 3, lines 6-7. The claimed apparatus is capable of detecting single base differences. See page 4, line 10 to page 5, line 5 and page 16, line 21 to page 17, line 6. Such meaning is also consistent with the prosecution history of all related applications, and is consistent with the meaning of the claim term during litigation of the patents issuing from the parent applications. See, for example, footnote 11 in document (3) identified in the Related Proceedings Appendix.

Therefore Stavrianopoulos fails to disclose or suggest an array of oligonucleotides having predetermined sequences wherein the complete sequence of each and every oligonucleotide on the array surface is known.

C. Stavrianopoulos Fails to Teach or Suggest an "array comprises at least two defined cells, the sequence of the oligonucleotides of a first cell is different from the sequence of the oligonucleotides of a second cell" according to Claim 17

Furthermore, Stavrianopoulos fails to disclose or suggest an array of oligonucleotides with predetermined sequences attached to the porous material, "wherein the array comprises at least two defined cells, the sequence of the oligonucleotides of a first cell is different from the sequence of the oligonucleotides of a second cell" according to claim 17.

In section 16, the examiner states "Further, the description by Stavrianopoulos of "various" single stranded analytes for use in an array for hybridization is reasonably interpreted as being different oligonucleotides, as claimed." However such position is untenable.

Reversal of the rejection of claim 17 is thus requested.

Claims 18-22 and 26-27 are dependent on claim 17 and so the rejection of these claims should also be reversed.

_Claims 23 and 86_

Claim 23 differs from claim 17 by requiring that "the oligonucleotides are covalently attached to the porous material". Claim 86 includes the same limitation.

In the final Office Action the examiner stated that Stavrianopoulos discloses covalent attachment of DNA (*"... covalently attached to the support after the glass has been treated with a silane linker for covalent attachment (col. 8, Example)"*, section 4 of final Office Action; *"... Stavrianopoulos teaches treatment of the array with a silane linker (the [g]amma-aminopropyltriethoxysilane of Example 1) for covalent attachment of DNA"*, section 18). These statements from the examiner are incorrect and a full technical response to them was provided on pages 9-10 of the appellant's response in November 2007 and in the appellant's supplemental response in December 2007.

The Advisory Action of December 21, 2007 suggests that the examiner accepted that the objection had been technically wrong but the rejection was maintained. For teaching of covalent attachment the examiner instead cited the disclosure at the end of column 4 in Matkovich.

The appellant does not believe that a skilled person who combined Stavrianopoulos and Matkovich (itself an unreasonable combination; see above argument relating to claims 17-21 and 26-27) would then select covalent attachment from the possibilities given in Matkovich. The end of column 4 states that chemical reactants can have different natures (*"ionic, molecular or macromolecular"*) and then states that various possible attachment techniques can be used (*"... by strong physical forces or by being bonded in some manner, such as covalent chemical coupling ..."*). The examiner has selected one of these possibilities but has not given any justification for making this particular selection.

As explained in the appellant's responses to the final Office Action, Stavrianopoulos was aiming for a charged surface so as to facilitate non-covalent retention of DNA, which is a poly-anionic substance. Example 1 in Stavrianopoulos used γ-amino-propyl-triethoxy-silane (col. 8, lines 23*ff*), but this silane is used for ionic bonding of nucleotides. The silane becomes attached to the glass surface and its amino group is left outward-facing. Thus the surface becomes covered in amino groups, which are protonated to leave multiple positively-charged amine groups exposed on the surface. The amine is linked via the silane's propyl group down to the silicon region of the surface. This situation is confirmed by Stavrianopoulos at lines 32-35 of col. 8: *"The resulting treated glass surface will now have available alkylamine thereon suitable for immobilizing or fixing any negatively charged polyelectrolytes applied thereto."* Thus the exposed amines form non-covalent bonds with random negative phosphate groups on a nucleic acid's backbone. The non-covalent nature of this binding chemistry is confirmed by Dawson *et al.,* 2005 filed with appellant's Amendment After Final dated November 20, 2007. A copy of Dawson is attached in the Evidence Appendix.

Later in Stavrianopoulos, Example 5 uses either an amino-substituted hydrophobic polymer (column 10, line 63) or poly-lysine (column 11, line 2) to treat the surface of polystyrene. The amino groups here again serve to give a positively-charged aminated surface, as confirmed by Dawson. Similarly, Example 6 mentions the use of 6-aminohexane (column 11, line 60) which, again, gives a positively-charged amine-covered surface. The next method described in Example 6 is confirmed at column 12, line 14, to give a "polyamine polymeric coating".

Thus Stavrianopoulos repeatedly chose to provide a cationic surface so as to facilitate non-covalent retention of anionic DNA (*i.e.* for *"fixing any negatively charged polyelectrolytes applied thereto"*; Stavrianopoulos, column 8, lines 32-35). The examiner's rejection gives no reasonable justification why a skilled person who looked to Matkovich would reject Stavrianopoulos's choice of charged surfaces for and would instead use covalent bonding. A person of ordinary skill would not arbitrarily select covalent attachment chemistry for an analyte that is intrinsically ionic in nature and that had been deliberately immobilized by Stavrianopoulos in a non-covalent manner.

"One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988).

"It is impermissible . . . simply to engage in a hindsight reconstruction of the claimed invention, using the applicant's [invention] . . . as a template and selecting elements from references to fill the gaps." *In re Gorman*, 933 F.2d 982, 987, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991).

The rejection of claims 23 and 86 should therefore be reversed.

*Claims 24 and 87*

Claim 24 differs from claim 23 by additionally specifying that the covalent attachment is "by a terminal nucleotide". Claim 87 differs from claim 86 in the same way.

In the final Office Action the examiner asserted that the attachment chemistry in Stavrianopoulos used *"covalent attachment ... which involves the binding with terminal nucleotide"* (section 4). As mentioned above, covalent attachment is neither an explicit nor implicit aspect of the attachment chemistry in Stavrianopoulos. This point seems to have been conceded in the Advisory Action, but the examiner turns instead to Matkovich for the teaching of covalent attachment (see above). Even if the skilled person had combined Stavrianopoulos and Matkovich, and had then selected covalent attachment from Matkovich's teaching (all of which is denied), the examiner did not show any reason why terminal covalent attachment would obviously have been chosen.

Covalent attachment of nucleic acids to solid supports does not inevitably occur through a terminal nucleotide. On the contrary, it is known that nucleic acids can attach to porous nylon membranes by cross-linking between thymine residues in DNA and surface amine groups in nylon. Moreover, a standard way of ensuring covalent binding of nucleic acids to a nylon membrane is to use UV irradiation which, again, causes thymine residues (and to a lesser extent other nucleotides) to react with amine groups on the membrane. Such thymine residues are

present along the length of a nucleic acid, and so standard covalent attachment of nucleic acids to porous membranes is specifically not *"by a terminal nucleotide"*. Indeed, UV-induced attachment can occur at multiple sites along a nucleotide, such that over-irradiation can destroy the ability of a nucleic acid to hybridize to targets. Thus the examiner has failed to provide even a *prima facie* case of obviousness against claims 24 and 87.

In addition, neither Stavrianopoulos nor Matkovich provides any enabling guidance for achieving covalent attachment of nucleic acids *"by a terminal nucleotide"*. As mentioned above, Stavrianopoulos never mentions covalent attachment and instead focuses on non-covalent attachment. Matkovich mentions the general possibility of covalent attachment but this simple disclosure (i) is in a document that deals with attachment of polypeptides not nucleic acids and (ii) is not a specific reference to terminal covalent attachment which, as explained above, differs significantly from the random covalent attachment that is usually used for nucleic acids. Even if the claimed invention were suggested by a combination of Stavrianopoulos and Matkovich, the combination does not lead to an enabling disclosure.

Furthermore, the examiner failed to give any weight to the advantages of using terminal covalent attachment in nucleic acid arrays. These advantages have been confirmed by others in the art after the instant invention was made, *e.g.* Dawson *et al.* noted in 2005 that in the array field *"... a single terminal covalent attachment is preferred for short oligonucleotides. This terminal covalent attachment allows the entire oligonucleotide to be available for hybridization and to withstand the high temperatures and salt concentrations often required during the stringent washing conditions in subsequent steps of microarray processing."* These advantages flow directly from the array synthesis methods used in the present application; they are not a feature of the attachments taught by either Stavrianopoulos or Matkovich.

Therefore the appellant requests reversal of the rejection of claims 24 and 87.

*Claim 25*

Claim 25 was rejected in section 6 of the final Office Action because "*Stavrianopoulos et al. teaches in situ techniques (col. 5, lines 41-46) for attaching the nucleotide sequence*".

The examiner is correct that the term "*in situ*" was used in Stavrianopoulos, but it was not used in a context that means that *"oligonucleotides are synthesized in situ"*, as required by claim 25. On the contrary, the term "*in situ*" is used to refer to the immobilisation of whole cells, such that hybridisation then occurs "*in situ*" within the cell. Column 5, line 43, specifically states that "the cell is fixed to the support" in these *in situ* techniques, rather than being any reference to *in situ* synthesis of oligonucleotides. Indeed, because Stavrianopoulos immobilizes analyte rather than an oligonucleotide probe, it would be impossible for the immobilized sequence to be synthesized *in situ* in Stavrianopoulos.

Therefore the appellant requests reversal of the rejection of claim 25.

## CONCLUSION

In view of the foregoing, it is respectfully submitted that the rejection of claims 17-27 and 86-87 is untenable and should be reversed.

Respectfully submitted,

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September 25, 2008

## VIII. CLAIMS APPENDIX

An appendix containing a copy of the claims involved in the appeal.

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Claim 17. Apparatus for analysing a polynucleotide, the apparatus comprising: a support having an impermeable surface; porous material attached to the impermeable surface; and an array of oligonucleotides with predetermined sequences attached to the porous material, wherein the array comprises at least two defined cells, the sequence of the oligonucleotides of a first cell is different from the sequence of the oligonucleotides of a second cell, and the oligonucleotides are shorter than the polynucleotide.

Claim 18. Apparatus of claim 17, wherein the porous material is a microporous material.

Claim 19. Apparatus of claim 17, wherein the support is made of a silicon oxide.

Claim 20. Apparatus of claim 19, wherein the support is made of glass.

Claim 21. Apparatus of claim 17, comprising between 72 and $1.1 \times 10^{12}$ cells.

Claim 22. Apparatus of claim 17, wherein each cell holds at least $3 \times 10^{-12}$ mmol of oligonucleotide.

Claim 23. Apparatus of claim 17, wherein the oligonucleotides are covalently attached to the porous material.

Claim 24. Apparatus of claim 23, wherein the oligonucleotides are covalently attached by a terminal nucleotide.

Claim 25. Apparatus of claim 17, wherein the oligonucleotides are synthesized *in situ*.

Claim 26. Apparatus of claim 17, wherein the apparatus is manufactured using a computer-controlled device.

Claim 27. Apparatus of claim 26, wherein the computer-controlled device is a printing device.

Claim 86. Apparatus for analysing a polynucleotide, the apparatus comprising: a support having an impermeable surface; porous material attached to the impermeable surface; and an array of oligonucleotides with predetermined sequences attached to the porous material, wherein the array comprises at least two defined cells, the sequence of the oligonucleotides of a first cell is different from the sequence of the oligonucleotides of a second cell, and the oligonucleotides are shorter than the polynucleotide, wherein the oligonucleotides are covalently attached to the porous material.

Claim 87. Apparatus of claim 86, wherein the oligonucleotides are covalently attached by a terminal nucleotide.

## IX. EVIDENCE APPENDIX

An appendix containing copies of any evidence submitted pursuant to §§ 1.130, 1.131 or 1.132 of this title or any other evidence entered by the examiner and relied upon by appellant in the appeal, along with a statement setting forth where in the record that evidence was entered in the record by the examiner. Reference to unentered evidence is not permitted in the brief. See §41.33 for treatment of evidence submitted after appeal. This appendix may also include copies of the evidence relied upon by the examiner as to grounds of rejection to be reviewed on appeal.

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(1) Stavrianopoulos et al. U.S. Patent No. 4,994,373

The reference is cited by the Examiner in the final Office Action dated August 23, 2007.

(2) Matkovich et al. U.S. Patent No. 4,828,386

The reference is cited by the Examiner in the final Office Action dated August 23, 2007.

(3) Dawson et al., Analytical Biochemistry 341 (2005) 352-360

Page 1 of the reference was submitted with appellant's Amendment After Final dated November 20, 2007 to support a statement by appellant in the remarks of the Amendment. The Advisory Action did not indicate whether or not the reference was entered. However the Examiner changed the basis of her rejection in the Advisory Action, therefore appellant believes that the reference was considered and entered by the Examiner.

## X. RELATED PROCEEDINGS APPENDIX

An appendix containing copies of decisions rendered by a court or the Board in any proceeding identified pursuant to paragraph (c)(1)(ii).

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(1) Memorandum Opinion on Claim Construction, Oxford Gene Technology Ltd. v. Affymetrix, Inc., Civil Action No. 99-348-JJF before the United States District Court for the District of Delaware, November 5, 2000.

(2) Order on Claim Construction, Oxford Gene Technology Ltd. v. Affymetrix, Inc., Civil Action No. 99-348-JJF before the United States District Court for the District of Delaware, November 5, 2000.

(3) Memorandum Opinion and Order on Claim Construction, Oxford Gene Technology Ltd. v. Mergen Ltd., et al., Civil Action No. 02-1695-KAJ before the United States District Court for the District of Delaware, 2004 WL 2211971, September 29, 2004.

(4) Opinion and Order on Motions for Summary Judgment, Oxford Gene Technology Ltd. v. Mergen Ltd., et al., Civil Action No. 02-1695-KAJ before the United States District Court for the District of Delaware, 345 F.Supp.2d. 444, November 19, 2004.

(5) Order on Motion for Reconsideration, Oxford Gene Technology Ltd. v. Mergen Ltd., et al., Civil Action No. 02-1695-KAJ before the United States District Court for the District of Delaware, 2005 WL 121797, January 7, 2005.

## IX. EVIDENCE APPENDIX

(1) Stavrianopoulos et al. U.S. Patent No. 4,994,373

United States Patent [19]
Stavrianopoulos et al.
[11] Patent Number: 4,994,373
[45] Date of Patent: Feb. 19, 1991

[54] METHOD AND STRUCTURES EMPLOYING CHEMICALLY-LABELLED POLYNUCLEOTIDE PROBES

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[21] Appl. No.: **385,986**

[22] Filed: **Jul. 20, 1989**

**Related U.S. Application Data**

[63] Continuation of Ser. No. 732,374, May 9, 1985, abandoned, which is a continuation-in-part of Ser. No. 461,469, Jan. 21, 1983, abandoned.

[51] **Int. Cl.**[5] .......................... **C12Q 1/68**; C07H 21/00; G01N 33/533

[52] **U.S. Cl.** .......................................... **435/6**; 435/7; 435/188; 435/296; 435/300; 435/4; 435/810; 436/94; 436/501; 436/524; 436/527; 436/531; 436/532; 436/800; 436/810; 526/27; 935/77; 935/78; 935/86; 935/87

[58] **Field of Search** .................. 536/27; 436/800, 810; 935/77, 78, 86, 87

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[57] **ABSTRACT**

Polynucleotide sequences in a sample of biological or nonbiological material are detected by a method involving fixing of the sequences on a solid support and forming an entity between the fixed sequences and chemically-labeled polynucleotide or oligonucleotide probes having a sequence complementary to the fixed sequence for determining the identification and/or presence of the target polynucleotide sequences. The chemical label covalently or noncovalently attached to the probe comprises a signalling moiety capable of generating a soluble signal detectable by spectrophotometric assay techniques.

**27 Claims, No Drawings**

# METHOD AND STRUCTURES EMPLOYING CHEMICALLY-LABELLED POLYNUCLEOTIDE PROBES

This is a continuation of applicants' U.S. patent application Ser. No. 06/732,374, filed May 9, 1985, now abandoned, which is a continuation-in-part of applicants' U.S. patent application Ser. No. 06/461,469, filed Jan. 21, 1983, now abandoned.

## TECHNICAL FIELD OF INVENTION

The present invention relates generally to the detection of genetic material by polynucleotide probes. More specifically, it relates to a method for quantifiably detecting a targeted polynucleotide sequence in a sample of biological and/or nonbiological material employing a probe capable of generating a soluble signal. The method and products disclosed herein in accordance with the invention are expected to be adaptable for use in many laboratory, industrial, and medical applications wherein quantifiable and efficient detection of genetic material is desired.

## BACKGROUND OF THE INVENTION

In the description, the following terms are employed:

Analyte—A substance or substances, either alone or in admixtures, whose presence is to be detected and, if desired, quantitated. The analyte may be a DNA or RNA molecule of small or high molecular weight, a molecular complex including those molecules, or a biological system containing nucleic acids, such as a virus, a cell, or group of cells. Among the common analytes are nucleic acids (DNA and RNA) or segments thereof, oligonucleotides, either single- or double-stranded, viruses, bacteria, cells in culture, and the like. Bacteria, either whole or fragments thereof, including both gram positive and gram negative bacteria, fungi, algae, and other microorganisms are also analytes, as well as animal (e.g., mammalian) and plant cells and tissues.

Probe—A labelled polynucleotide or oligonucleotide sequence which is complementary to a polynucleotide or oligonucleotide sequence of a particular analyte and which hybridizes to said analyte sequence.

Label—That moiety attached to a polynucleotide or oligonucleotide sequence which comprises a signalling moiety capable of generating a signal for detection of the hybridized probe and analyte. The label may consist only of a signalling moiety, e.g., an enzyme attached directly to the sequence. Alternatively, the label may be a combination of a covalently attached bridging moiety and signalling moiety or a combination of a non-covalently bound bridging moiety and signalling moiety which gives rise to a signal which is detectable, and in some cases quantifiable.

Bridging Moiety—That portion of a label which on covalent attachment or non-covalent binding to a polynucleotide or oligonucleotide sequence acts as a link or a bridge between that sequence and a signalling moiety.

Signalling Moiety—That portion of a label which on covalent attachment or non-covalent binding to a polynucleotide or oligonucleotide sequence or to a bridging moiety attached or bound to that sequence provides a signal for detection of the label.

Signal—That characteristic of a label or signalling moiety that permits it to be detected from sequences that do not carry the label or signalling moiety.

The analysis and detection of minute quantities of substances in biological and non-biological samples has become a routine practice in clinical, diagnostic and analytical laboratories. These detection techniques can be divided into two major classes: (1) those based on ligand-receptor interactions (e.g., immunoassay-based techniques), and (2) those based on nucleic acid hybridization (polynucleotide sequence-based techniques).

Immunoassay-based techniques are characterized by a sequence of steps comprising the noncovalent binding of an antibody and antigen complementary to it. See, for example, T. Chard, *An Introduction To Radioimmunoassay And Related Techniques* (1978).

Polynucleotide sequence-based detection techniques are characterized by a sequence of steps comprising the non-covalent binding of a labelled polynucleotide sequence or probe to a complementary sequence of the analyte under hybridization conditions in accordance with the Watson-Crick base pairing of adenine (A) and thymine (T), and guanine (G) and cytosine (C), and the detection of that hybridization. [M. Grunstein and D. S. Hogness, "Colony Hybridization: A Method For The Isolation Of Cloned DNAs That Contain A Specific Gene", *Proc. Natl. Acad. Sci. U.S.A.*, 72, pp. 3961–65 (1975)]. Such polynucleotide detection techniques can involve a fixed analyte [see, e.g., U.S. Pat. No. 4,358,535 to Falkow et al], or can involve detection of an analyte in solution [see U.K. patent application No. 2,019,408 A].

The primary recognition event of polynucleotide sequence-based detection techniques is the non-covalent binding of a probe to a complementary sequence of an analyte, brought about by a precise molecular alignment and interaction of complementary nucleotides of the probe and analyte. This binding event is energetically favored by the release of non-covalent bonding free energy, e.g., hydrogen bonding, stacking free energy and the like.

In addition to the primary recognition event, it is also necessary to detect when binding takes place between the labelled polynucleotide sequence and the complementary sequence of the analyte. This detection is effected through a signalling step or event. A signalling step or event allows detection in some quantitative or qualitative manner, e.g., a human or instrument detection system, of the occurrence of the primary recognition event.

The primary recognition event and the signalling event of polynucleotide sequence based detection techniques may be coupled either directly or indirectly, proportionately or inversely proportionately. Thus, in such systems as nucleic acid hybridizations with sufficient quantities of radiolabeled probes, the amount of radio-activity is usually directly proportional to the amount of analyte present. Inversely proportional techniques include, for example, competitive immunoassays, wherein the amount of detected signal decreases with the greater amount of analyte that is present in the sample.

Amplification techniques are also employed for enhancing detection wherein the signalling event is related to the primary recognition event in a ratio greater than 1:1. For example, the signalling component of the assay may be present in a ratio of 10:1 to each recognition component, thereby providing a 10-fold increase in sensitivity.

A wide variety of signalling events may be employed to detect the occurrence of the primary recognition

event. The signalling event chosen depends on the particular signal that characterizes the label or signalling moiety of the polynucleotide sequence employed in the primary recognition event. Although the label may only consist of a signalling moiety, which may be detectable, it is more usual for the label to comprise a combination of a bridging moiety covalently or non-covalently bound to the polynucleotide sequence and a signalling moiety that is itself detectable or that becomes detectable after further modification.

The combination of bridging moiety and signalling moiety, described above, may be constructed before attachment or binding to the sequence, or it may be sequentially attached or bound to the sequence. For example, the bridging moiety may be first bound or attached to the sequence and then the signalling moiety combined with that bridging moiety. In addition, several bridging moieties and/or signalling moieties may be employed together in any one combination of bridging moiety and signalling moiety.

Covalent attachment of a signalling moiety or bridging moiety/signalling moiety combination to a sequence is exemplified by the chemical modification of the sequence with labels comprising radioactive moieties, fluorescent moieties or other moieties that themselves provide signals to available detection means or the chemical modification of the sequence with at least one combination of bridging moiety and signalling moiety to provide that signal.

Non-covalent binding of a signalling moiety or bridging moiety/signalling moiety to a sequence involve the non-covalent binding to the sequence of a signalling moiety that itself can be detected by appropriate means, i.e., or enzyme, or the non-covalent binding to the sequence of a bridging moiety/signalling moiety to provide a signal that may be detected by one of those means. For example, the label of the polynucleotide sequence may be a bridging moiety non-covalently bound to an antibody, a fluorescent moiety or another moiety which is detectable by appropriate means. Alternatively, the bridging moiety could be a lectin, to which is bound another moiety that is detectable by appropriate means.

There are a wide variety of signalling moieties and bridging moieties that may be employed in labels for covalent attachment or non-covalent binding to polynucleotide sequences useful as probes in analyte detection systems. They include both a wide variety of radioactive and non-radioactive signalling moieties and a wide variety of non-radioactive bridging moieties. All that is required is that the signalling moiety provide a signal that may be detected by appropriate means and that the bridging moiety, if any, be characterized by the ability to attach covalently or to bind non-covalently to the sequence and also the ability to combine with a signalling moiety.

Radioactive signalling moieties and combinations of various bridging moieties and radioactive signalling moieties are characterized by one or more radioisotopes such as $^{32}P$, $^{131}I$, $^{14}C$, $^{3}H$, $^{60}Co$, $^{59}Ni$, $^{63}Ni$ and the like. Preferably, the isotope employed emits $\beta$ or Y radiation and has a long half life. Detection of the radioactive signal is then, most usually, accomplished by means of a radioactivity detector, such as exposure to a film.

The disadvantages of employing a radioactive signalling moiety on a probe for use in the identification of analytes are well known to those skilled in the art and include the precautions and hazards involved in handling radioactive material, the short life span of such material and the correlatively large expenses involved in use of radioactive materials.

Non-radioactive signalling moieties and combinations of bridging moieties and non-radioactive signalling moieties are being increasingly used both in research and clinical settings. Because these signalling and bridging moieties do not involve radioactivity, the techniques and labelled probes using them are safer, cleaner, generally more stable when stored, and consequently cheaper to use. Detection sensitivities of the non-radioactive signalling moieties also are as high or higher than radiolabelling techniques.

Among the presently preferred non-radioactive signalling moieties or combinations of bridging/signalling moieties useful as non-radioactive labels are those based on the biotin/avidin binding system. [P. R. Langer et al., "Enzymatic Synthesis Of Biotin-Labeled Polynucleotides: Novel Nucleic Acid Affinity Probes", *Proc. Natl. Acad. Sci. U.S.A.*, 78, pp. 6633–37 (1981); J. Stavrianopoulos et al., "Glycosylated DNA Probes For Hybridization/Dection Of Homologous Sequences", presented at the Third Annual Congress For Recombinant DNA Research (1983); R. H. Singer and D. C. Ward, "Actin Gene Expression Visualized In Chicken Muscle Tissue Culture By Using In Situ Hybridization With A Biotinated Nucleotide Analog", *Proc. Natl. Acad. Sci. U.S.A.*, 79, pp. 7331–35 (1982)]. For a review of non-radioactive signalling and bridging/signalling systems, both biotin/avidin and otherwise, see D. C. Ward et al., "Modified Nucleotides And Methods Of Preparing And Using Same", European Patent application No. 63879.

Generally, the signalling moieties employed in both radioactive and non-radioactive detection techniques involve the use of complex methods for determining the signalling event, and/or supply only an unquantitable positive or negative response. For example, radioactive isotopes must be read by a radioactivity counter; while signalling moieties forming insoluble "signals", i.e., precipitates, certain fluorescers, and the like [see, e.g., David et al., U.S. Pat. No. 4,376,100] only provide detection not quantitation of the analyte present in the tested sample.

One step toward facilitating rapid and efficient quantitation as well as detection of the hybridization event was the work of Heller et al. in European Patent Application Nos. 70685 and 70687 which describe the use of a signalling moiety which produces a soluble signal for measurable detection by a spectrophotometer. These European patent applications disclose the use of two different probes complementary to different portions of a gene sequence, with each probe being labelled at the end which will abut the other probe upon hybridization. The first probe is labelled with a chemiluminescent complex that emits lights of a specific wavelength. The second probe is labelled with a molecule that emits light of a different wavelength measurable by spectrophotometry when excited by the proximity of the first signalling moiety. However, this technique is performed in solution and can generate false positive results in the absence of the analyte if the two probes happen to approach too closely in solution and react with each other.

Similarly, U.K. Patent Application Ser. No. 2,019,408A, published Oct. 31, 1979, discloses a method for detecting nucleic acid sequences in solution by employing an enzyme-labelled RNA or DNA probe

which, upon contact with a chromogen substrate, provides an optically readable signal. The analytes may be separated from contaminants prior to hybridization with the probe, or, alternatively, the hybrid probe-analyte may be removed from solution by conventional means, i.e., centrifugation, molecular weight exclusion, and the like. Like Heller's technique, this method is performed in solution.

There remains therefore a need in the art for a reliable, simple and quantifiable technique for the detection of analytes of interest in biological and non-biological samples.

## SUMMARY OF THE INVENTION

The invention provides a solution for the disadvantages of presently available methods of detecting analytes by a novel combination of hybridization and immunological techniques. In the present invention, chemically labelled polynucleotide or oligonucleotide probes are employed to detect analytes by having the capacity to generate a reliable, easily quantifiable soluble signal.

Analytes to be detected by the detection processes of this invention may be present in any biological or non-biological sample, such as clinical samples, for example, blood urine, feces, saliva, pus, semen, serum, other tissue samples, fermentation broths, culture media, and the like. If necessary, the analyte may be pre-extracted or purified by known methods to concentrate its nucleic acids. Such nucleic acid concentration procedures include, for example, phenol extraction, treatment with chloroform-isoamyl alcohol or chloroform-octanol, column chromatography (e.g., Sephadex, hydroxyl apatite), and CsCl equilibrium centrifugation. The analyte, separated from contaminating materials, if present, is according to the present invention, fixed in hybridizable form to a solid support.

Analytes in a biological sample are preferably denatured into single-stranded form, and then directly fixed to a suitable solid support. Alternatively, the analyte may be directly fixed to the support in double-stranded form, and then denatured. The present invention also encompasses indirect fixation of the analyte, such as in situ techniques where the cell is fixed to the support and sandwich hybridization techniques where the analyte is hybridized to a polynucleotide sequence that is fixed to the solid support. It is preferred that the solid support to which the analyte is fixed be non-porous and transparent, such as glass, or alternatively, plastic, polystyrene, polyethylene, dextran, polypropylene and the like. Conventional porous materials, e.g., nitrocellulose filters, although less desirable for practice of the method of the present invention, may also be employed as a support.

It is also highly desirable that the analyte be easily fixed to the solid support. The capability to easily fix the analyte to a transparent substrate would permit rapid testing of numerous samples by the detection techniques described herein.

Chemically-labeled probes are then brought into contact with the fixed single-stranded analytes under hybridizing conditions. The probe is characterized by having covalently attached to it a chemical label which consists of a signalling moiety capable of generating a soluble signal. Desirably, the polynucleotide or oligonucleotide probe provides sufficient number of nucleotides in its sequence, e.g., at least about 25, to allow stable hybridization with the complementary nucleotides of the analyte. The hybridization of the probe to the single-stranded analyte with the resulting formation of a double-stranded or duplex hybrid is then detectable by means of the signalling moiety of the chemical label which is attached to the probe portion of the resulting hybrid. Generation of the soluble signal provides simple and rapid visual detection of the presence of the analyte and also provides a quantifiable report of the relative amount of analyte present, as measured by a spectrophotometer or the like.

The method of the present invention involving the colorimetric or photometric determination of the hybridized probes employs as the signalling moiety reagents which are capable of generating a soluble signal, e.g., a color change in a substrate in solution. Preferable components of the signalling moiety include enzymes, chelating agents and co-enzymes, which are able to generate colored or fluorescent soluble signals. Specifically, certain chromogens upon contact with certain enzymes are utilizable in the method of the present invention. The following Table I lists exemplary components for the signalling moiety of the present invention. Each chromogen listed is reactive with the corresponding enzyme to produce a soluble signal which reports the presence of the chemically-labeled probe analyte hybrid. The superscript notation (*) indicates that the chromogen fluoresces, rather than produces a color change.

TABLE I

| ENZYME | CHROMOGEN |
|---|---|
| alkaline phosphatase or acid phosphatase | *4-Methylumbelliferyl phosphate |
| | *bis (4-Methylumbelliferyl phosphate |
| | 3-0-methylfluorescein. |
| | *Flavone-3-diphosphate triammonium salt |
| | p-nitrophenyl phosphate 2Na. |
| peroxidase | *Tyramine hydrochloride |
| | *3-(p-hydroxyphenyl) Propionic acid |
| | *p-Hydroxyphenethyl alcohol |
| | 2,2'-Azino-Di-3-Ethylbenzthiazoline sulfonic acid (ABTS) |
| | ortho-phenylenediamine 2HCl |
| | 0-dianisidine |
| | *5-aminosalicylic acid |
| | p-cresol |
| | 3,3'-dimethyloxybenzidine |
| | 3-methyl-2-benzothiazoline hydrazone |
| | tetramethyl benzidine |
| β-D-galactosidase | 0-nitrophenyl β-D-galactopyranoside |
| | 4-methylumbelliferyl-β-D-galactoside |
| glucose-oxidase | ABTS |

As another aspect of the present invention, the signalling moiety may be attached to the probe through the formation of a bridging entity or complex. Likely candidates for such a bridging entity would include a biotin-avidin bridge, a biotin-streptavidin bridge, or a sugar-lectin bridge.

Once the fixed probe-analyte hybrid is formed, the method may further involve washing to separate any non-hybridized probes from the area of the support.

The signalling moiety may also be attached to the probe through the bridging moiety after the washing step to preserve the materials employed. Thereafter, another washing step may be employed to separate free signalling moieties from those attached to the probe through the bridging moiety.

Broadly, the invention provides hybridization techniques which provide the same benefits as enzyme linked immunosorbent assay techniques, i.e., the qualitative and quantitative determination of hybrid formation through a soluble signal. Various techniques, depending upon the chemical label and signalling moiety of the probe, may be employed to detect the formation of the probe-analyte hybrid. It is preferred, however, to employ spectrophotometric techniques and/or colorimetric techniques for the determination of the hybrid. These techniques permit not only a prompt visual manifestation of the soluble signal generated by the signalling moiety on the double-stranded hybrid, but also permit the quantitative determination thereof, i.e., by the enzymatic generation of a soluble signal that can be quantitatively measured.

Yet another aspect of the method of the present invention involves generating the soluble signal from the probe-analyte hybrid in a device capable of transmitting light therethrough for the detection of the signal by spectrophotometric techniques. Examples of devices useful in the spectrophotometric analysis of the signal include conventional apparatus employed in diagnostic laboratories, i.e., plastic or glass wells, tubes, cuvettes or arrangements of wells, tubes or cuvettes. It may also be desirable for both the solid support to which the analyte is fixed and the device to be composed of the same material, or for the device to function as the support in addition to facilitating spectrophotometric detection.

A further aspect of the present invention provides products useful in the disclosed method for detection of a polynucleotide sequence. Among these products is a device containing a portion for retaining a fluid. Such portion contains an immobilized polynucleotide sequence hybridized to a polynucleotide or oligonucleotide probe. The probe, as described above, has covalently attached thereto a chemical label including a signalling moiety capable of generating a soluble signal. Also part of the device is a soluble signal, preferably a colored or fluorescent product, generatable by means of the signalling moiety. The portion of the device for containing the fluid is desirably a well, a tube, or a cuvette. A related product of the invention is an apparatus comprising a plurality of such devices for containing a fluid, in which at least one such device contains the above-described immobilized polynucleotide sequence, polynucleotide or oligonucleotide probe, signalling moiety, and soluble signal. Additionally the present invention provides for the novel product of a non-porous solid support to which a polynucleotide is directly fixed in hybridizable form. Such a fixed sequence may be hybridized to another polynucleotide sequence having covalently attached thereto a chemical label including a signalling moiety capable of generating a soluble signal. As indicated above, the support is preferably transparent or translucent. Such products could be advantageously employed in diagnostic kits and the like.

Other aspects and advantages of the present invention will be readily apparent upon consideration of the following detailed description of the preferred embodiments thereof.

## DETAILED DESCRIPTION

The following examples are illustrative of preferred embodiments of the method of the present invention. Specifically referred to therein are methods for fixing the analyte to a non-porous solid support, as well as illustrations of the use of soluble signals in polynucleotide probes as discussed above.

### EXAMPLE 1

For purposes of the present invention, an analyte is immobilized on a solid support, preferably a non-porous translucent or transparent support. To effect easy fixing of a denatured single-stranded DNA sequence to a glass support, an exemplary "fixing" procedure may involve pretreating the glass by heating or boiling for a sufficient period of time in the presence of dilute aqueous nitric acid. Approximately forty-five minutes in 5% dilute acid should be adequate to leach boron residues from a borosilicate glass surface. The treated glass is then washed or rinsed, preferably with distilled water, and dried at a temperature of about 115° C., for about 24 hours. A 10 percent solution of gamma-aminopropyltriethoxysilane, which may be prepared by dissolving the above-identified silane in distilled water followed by addition of 6N hydrochloric acid to a pH of about 3.45, will then be applied to the glass surface. The glass surface is then incubated in contact with the above-identified silane solution for about 2-3 hours at a temperature of about 45° C. The glass surface is then washed with an equal volume of water and dried overnight at a temperature of about 100° C. The resulting treated glass surface will now have available alkylamine thereon suitable for immobilizing or fixing any negatively charged polyelectrolytes applied thereto. [See Weetal, H. H. and Filbert, A. M., "Porous Glass for Affinity Chromatography Applications", *Methods in Enzymology*, Vol. XXXIV, Affinity Techniques Enzyme Purification: Part B. pp. 59-72, W. B. Jakoby and M. Wilchek, eds.]

Such treated glass could then be employed in the method of the invention. For example, glass plates provided with an array of depressions or wells would have samples of the various denatured analytes deposited therein, the single-stranded analytes being fixed to the surfaces of the wells. Thereupon, polynucleotide probes provided with a chemical label may be deposited in each of the wells for hybridization to any complementary single-stranded analyte therein. After washing to remove any non-hybridized probe, the presence of any hybrid probe-analyte is then detectable. One detection technique as described herein involves the addition of an enzyme-linked antibody or other suitable bridging entity of the label for attachment to the probe. Subsequently a suitable substrate is added to elicit the soluble signal, e.g., a color change or chemical reaction, which is then measured colorimetrically or photometrically.

### EXAMPLE 2

A glass surface treated as described in Example 1 can be employed in the method of the present invention, wherein glucosylated DNA is employed as the labelled probe, and the signalling moiety comprises the combination of acid phosphatase and its substrate paranitrophenylphosphate.

In this procedure, glucosylated bacteriophage $T_4$ DNA, isolated from E. coli CR63 cultures infected with phage $T_4$ AM82 [44−62−] and purified to be free of chromosomal DNA, or non-glucosylated, highly puri-

fied calf thymus DNA is delivered in 100 μl portions to treated glass tubes in triplicate set. After 15–30 minutes at room temperature, the solution is removed and the tubes rinsed generously with PBS.Mg++ buffer [100 mM Na-K-$PO_4$, pH 6.5, 150 mM NaCl and 10 mM $MgCl_2$].

One set of tubes is checked for the presence of DNA by staining with ethidium bromide [100 μl of 1 mg/ml solution, 30 minutes in the dark, at room temperature]. The staining solution is removed and the tubes rinsed and checked by UV light. Both glucosylated labelled and unlabelled DNA "probe" bound to the activated glass surface by the observed red fluorescence characteristic of ethidium bromide.

To another set of tubes is delivered fluorescein-labelled ConA [100 μl of 0.1 mg/ml in PBS.Mg++ buffer]. The Concanavalin A [ConA] is obtained and solubilized in 2.0M NaCl at a concentration of 50 mg/ml, and fluorescein-labelled by reacting ConA with fluorescein isothiocyanate at an FITC to protein molar ratio of 3 to 1 in 0.1M sodium borate solution at a pH of 9.2 and at a temperature of 37° C. for 60 minutes. Any unreacted FITC is removed by gel filtration on Sephadex G-50. After 60 minutes at room temperature, the solution is removed and the tubes rinsed and checked under UV light. ConA bound only to glucosylated DNA in tubes containing $T_4$ DNA.

To the third set of tubes is delivered 100 μl of unlabeled ConA in PBS.Mg++ buffer. After 60 minutes at room temperature, the tubes are rinsed free of ConA with 0.2M Imidazole buffer pH 6.5.

Acid phosphatase is then added [0.005 units in 100 μl at 0.2 percent phosphatase-free BSA] and the tubes are incubated at room temperature for 30 minutes. After rinsing with 0.15M NaCl to remove any unbound enzyme, 0.1 mM paranitrophenylphosphate in 0.2M imidazole at pH 6.5 is added and incubation continued for 60 minutes at 37° C. The enzyme reaction is terminated by adding 1.0 ml of 0.5 percent sodium bicarbonate and absorbance is determined at $A_{300}$.

The resulting observed test results indicate that acid phosphatase, one component of the signalling moiety gives a positive visible color reaction, upon reaction with its chromogen, only in tubes containing "probe" $T_4$ DNA and bridging moiety, ConA, but is washed off from the tubes which contain only ConA or ConA and calf thymus DNA.

## EXAMPLE 3

In an example of the method of the present invention, phage lambda DNA was employed as the analyte, glucosylated DNA as the labelled probe, ConA as the bridging entity and alkaline phosphatase with paranitrophenylphosphate as the signalling moiety. Bacteriophage lambda, obtained by heat induction of *E. coli* stain W3350 lysogenic for $\lambda C_1 857$ phage, was employed for the preparation of phage lambda DNA. In these tests, the analyte, phage lambda DNA, was immobilized on an activated glass surface according to the following procedure. After rinsing with buffer, glass tubes were coated with 100 μl of coating solution [50 percent formamide, 5X SSC, 100 μg salmon sperm DNA 0.2 percent polyvinyl pyrrolidone, 0.1 percent Triton X-100, 0.2 percent BSA and 0.05 percent SDS] at 42° C. for 90–120 minutes. The coating solution was removed and the surface was covered with 100 μl of coating solution containing phage lambda DNA.

Phage lamba DNA employed as the probe is nick translated with maltose-triose dUTP to introduce glucosyl residues into the DNA. The glucosylated minutes and rapidly cooled in ice bath immediately before use. The tubes were then incubated with probe at 42° C. for 24 hours. The solution was removed and tubes were rinsed with PBS.Mg++ buffer. As described above in example 2, ConA is added to the tubes in PBS.Mg++ buffer. After 60 minutes at room temperature the tubes are rinsed with 0.2M Imidazole buffer.

Also as described in Example 2, the signalling moiety components, acid phosphatase and paranitrophenyl phosphate, are sequentially introduced into the tubes, to generate the detectable soluble signal. In these tests, the glucosyl moiety of the DNA probe is one bridging moiety of the chemical label, and reacts with and is strongly attracted to the second bridging moiety, ConA. The results indicated that acid phosphatase was not washed off from the tubes which contained glucosylated probe, whereas tubes containing non-labelled probe did not show any enzyme activity.

## EXAMPLE 4

As in the above example employing a glucosylated DNA as the labelled probe, wherein the glucosyl moiety serves as part of the chemical label, comparable results may also be achieved by employing a biotin-labeled DNA probe. When biotin is employed as a bridging moiety of the chemical label of the DNA probe, the presence of the biotin-labeled DNA probe would be elicited or detected by means of an avidin or streptavidin-linked enzyme, since avidin is strongly reactive with or strongly bonds to biotin.

For example, a biotin-labeled DNA probe would readily be detected by an enzyme complex of the character avidin-biotin-alkaline phosphatase. More specifically, the presence of the biotin-labeled DNA probe would readily be detected by contacting the hybrid containing the biotin-labeled probe with the enzyme complex avidin-biotin-alkaline phosphatase, and bringing the resulting probe and avidin-biotin-alkaline phosphatase complex into contact with a suitable substrate which, upon contact with the enzyme, would produce a soluble signal that would be readily noticed or be capable of being determined, both qualitatively and quantitatively, by photometric and/or colorimetric means. If desired, instead of an avidin-biotin-enzyme complex, there could be used an antibody to biotin for attachment to the biotin moiety of the biotin-labeled DNA probe, followed by a complex comprising anti-antibody-enzyme in the manner described above.

## EXAMPLE 5

The advantages of this invention are also obtainable when the probe is immobilized on a non-porous plastic surface. When a plastic surface is employed, it is sometimes desirable to increase the effectiveness or uniformity of the fixation by pretreating the plastic surface.

Because polystyrene from various batches or sources exhibits different binding capacities, the adherence or fixing of DNA to a polystyrene surface is improved by treating the surface with an amino-substituted hydrophobic polymer or material. Previous experiments demonstrated that addition of duodecadiamine (DDA) to polystyrene resulted in an uniform binding coefficient of polystyrene plates of different batches. Another technique for improving the fixing or uniformity of the

plastic surface for fixing DNA involves treatment of the surface with polylysine (PPL).

In tests involving the fixing of DNA to a plastic surface, biotinylated DNA (b-DNA) was denatured and aliquoted into Dynatech, Immulon II TM removable wells. Samples were allowed to dry onto the plastic surface at 37° C. The amount of bound b-DNA was determined by sequential addition of goat anti-biotin antibody and rabbit anti-goat antibody complexed to the signalling moiety, alkaline phosphatase, followed by development with p-nitrophenyl phosphate in diethanolamine buffer, pH 9.6. Enzymatic activity was monitored at 405 nm utilizing the automatic Dynatech Micro ELISA Scanner. This procedure enables quantitation of the amount of bound DNA and therefore the degree of biotinylation. To increase the sensitivity of detection, a fluorogenic substrate such as 4-methylumbelliferyl-phosphate, or its analogues, with companion enzymes, may be used.

In a further example of the method, denatured adenovirus 2 DNA, the analyte, was bound to polystyrene plates as described above. After blocking with Denhardt's formamide blocking buffer, several biotinylated probes, b-adeno-2-DNA and lambda DNA were hybridized to the immobilized DNA. To one set of immobilized DNA, no probe was added. The extent of hybridization was determined by means of the antibody-enzyme reaction as described above. It was observed that only the homologous adeno-2 probe hybridized. This technique demonstrated that in vitro hybridization under these conditions is specific and can be monitored quantitatively by the method of the present invention.

Other methods for enabling fixation of single-stranded analyte to a solid support for use in the method of the present invention include the following.

## EXAMPLE 6

In further tests, radioactively-labeled DNA was prepared by nick translation with [$^3$H]dATP. The labelled, non-biotinylated denatured DNA [2000 ng to 5 ng] was applied to DDA-coated polystyrene plates. The test samples or plates were not allowed to dry. After incubation at 37° C. for periods of 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, and 18 hours, samples were counted. Binding was maximal after two hours of incubation, however, 50 percent of the originally applied DNA bound regardless of the concentration, thereby indicating that there is an equilibrium between bound and unbound DNA.

In other tests, polystyrene microfilter wells were nitrated using the procedure of Filipsson and Hornby, *Biochem. J.* 120, 215 (1970). The polystyrene wells were immersed for 20 minutes in a mixture of concentrated nitric and sulfuric acid [41 percent, v/v] cooled to 0° C. The wells were then washed thoroughly with water and subsequently heated to 70° C. in a 6 percent solution of sodium dithionate in 2M potassium hydroxide. After 4 hours, the wells were washed thoroughly with 0.5M hydrochloric acid and distilled water.

To produce 6-aminohexane linked polystyrene, 6-amino-caproic acid-N-hydroxysuccinimide ester.hydrobromide [5 mg thereof dissolved in 0.2M dimethylformamide prepared by reacting 6-aminocaproic acid.hydrobromide with N-hydroxysuccinimide and dicyclohexyl carbodiimide in dimethylformamide and recrystallized from isopropyl alcohol] was added to 0.1M sodium borate [0.4 ml]. Amino-derivitized polystyrene microfilter wells filled with this solution were allowed to react at room temperature for 4 hours and then washed thoroughly with distilled water. The resulting treated wells absorbed H-labeled DNA from aqueous solution at pH less than 9.5.

An improved capability for fixing or immobilization of DNA to non-porous siliceous solid supports, such as glass and plastic, is also provided by treatment with a coating of an epoxy resin. For example, treatment of glass or polystyrene surfaces with commercially available epoxy glues, such as a solution of epoxy glue in ethanol [1 percent w/v] serves this purpose. These epoxy solutions are applied to the surfaces or wells, and the solvent, ethanol, evaporated thereupon at a temperature of 37° C., thereby providing a polyamine polymeric coating on the treated surface. These surfaces were found to absorb $^3$H-labeled DNA from aqueous solution at pH less than 9.5.

## EXAMPLE 7

Yet another example of the method of the present invention, including fixing the polynucleotide analyte sequence directly to a non-porous solid support, such as a conventional microtiter well, may be performed according to the procedures outlined below.

Conventional microtiter well plates can be pre-rinsed with 1M ammonium acetate ($NH_4OAc$), in an amount of 200 μls/well. Analyte DNA would be diluted to 10–200 ng/50 ul in water or 10 mM Tris-HCl at pH 7.5 and 1 mM EDTA(TE). After boiling for 5 minutes and quick cooling in ice water, an equal volume of 2M $NH_4OAc$ would be added and 50 ul of analyte DNA is added per well, giving 5–100 ng of analyte DNA per well. After open plate incubation for 2 hours at 37° C., the wells can be sealed and plates stored at 4° C. Alternatively, open plates can be incubated at 37° C. until the wells are dry, at which point the plates can be sealed, and stored at 4° C. for up to one-two months. Single-stranded analyte DNA is now fixed to the wells.

An alternative method to denature and then fix the analyte DNA to the well is to add 50 ul of DNA in TE to wells at a concentration of 10–200 ng/50 ul. After adding 25 ul at 0.9N NaOH and mixing, the plates can be incubated for 10 minutes at room temperature. After adding 25 ul of 4M $NH_4OAc$, the open plate may be incubated at 37° C. for 4 hours or until dry and the plates sealed and stored at 4° C. until ready to use.

To prepare the plates for hybridization, the wells would be rinsed twice with 0.3m NaCl, 0.03m sodium citrate (2X SSC) (200 ul/well) buffer regardless of whether the plate was dried or not. Preferably, the wells can be rinsed once with 2X SSC/1% Triton X-100 after the two 2X SSC rinses. Plates should be blotted on absorbent paper before beginning each rinse.

To hybridize the fixed analyte with a probe, the following protocol would be followed. A nick translated probe would be heat denatured and added to a hybridization solution containing 30% formamide (deionized), 2X–4X SSPE (20X SSPE=3.6M NaCl, 0.2M $NaPO_4$, pH 7.4, 0.02M EDTA) depending on the GC content of probe, 0.1% SDS, and 5.0% dextran sulfate to give a final concentration of 0.2–1.0 ug probe/ml. An alternative hybridization solution contains 30% formamide (deionized), 2X–4X SSPE, 1.0% Triton X-100, and 5.0% dextran sulfate and 0.2–1.0 ug probe/ml. 100 ul of the selected hybridization mixture is added to each well. After sealing the plates, they are incubated at 37° C. for a desired time.

The hybridization solution is poured out, or collected by aspiration for reuse if desired. The plates are rinsed twice with 2X SSC and 0.1% SDS or 2X SSC and 0.1% Triton X-100 according to whether the first or second hybridization solution identified above was employed. At this point two to four stringency rinses of SSC and detergent are preferably performed by heating the buffer to the desired temperature and adding it hot to the wells. Formamide and low SSC or SSPE can be used at 37°-40° C. to achieve the desired stringency. Following stringency washes, wells are rinsed twice with 1X SSC or 1X SSC and 0.1% Triton X-100, and the plates are now ready for detection.

Detection of the fixed hybridized analyte-probe according to the invention may employ the procedure for commercially available ELISA assays using the sensitive DETEK ® 1-alkaline phosphatase or DETEK ® 1-horseradish peroxidase assays (Enzo Biochem, Inc.). Beginning at the blocking procedure, the standard method is employed except that after blocking, no rinsing step is used. Complex diluted in 1X complex dilution buffer is thereafter added as taught in these commercially available assays.

As will be apparent to those skilled in the art in the light of the foregoing disclosure, many alterations, modifications and substitutions are possible in the practice of this invention, without departing from the spirit or scope thereof. Consequently, only such limitations as appear in the appended claims should be placed upon the scope of the invention.

What is claimed is:

1. A method for detecting a polynucleotide sequence which comprises:

fixing said polynucleotide sequence to a solid support which comprises or is contained within a transparent or translucent, non-porous system, such that a single-strand of the polynucleotide is capable of hybridizing to complementary nucleic acid sequences;

forming an entity comprising said polynucleotide sequence hybridized to a polynucleotide or oligonucleotide probe, said probe having attached thereto a chemical label further comprising a signalling moiety capable of generating a soluble signal; and

generating and detecting said soluble signal.

2. The method according to claim 1, wherein said detecting step comprises spectrophotometric techniques.

3. The method according to claim 1, wherein said soluble signal is selected from the group consisting of a colored product, a chemiluminescent product and a fluorescent product.

4. The method according to claim 1, wherein said signalling moiety is selected from the group consisting of an enzyme, a chelating agent and a co-enzyme.

5. The method according to claim 1, wherein said solid support is selected from the group consisting of glass, plastic, polystyrene, polyethylene, dextran and polypropylene.

6. The method according to claim 1, wherein said polynucleotide sequence is directly fixed to said solid support.

7. The method according to claim 6, wherein said polynucleotide sequence is fixed to said solid support in single stranded form.

8. The method according to claim 1, wherein said signalling moiety is attached to said polynucleotide or oligonucleotide probe through the formation of a complex.

9. The method according to claim 8, wherein said complex is selected from the group consisting of biotin and avidin, biotin and streptavidin, and a sugar and a lectin.

10. The method according to claim 1, wherein said forming step further comprises washing to remove said polynucleotide or oligonucleotide probes that do not form said entity.

11. The method according to claim 10, wherein said forming step further comprises attaching said signalling moiety to said polynucleotide or oligonucleotide probe after said washing step.

12. The method according to claim 11, which further comprises separating free signalling moieties from said attached signalling moieties.

13. The method according to claim 1, wherein said detecting step further comprises generating said soluble signal in a device capable of transmitting light therethrough for the detection of said soluble signal by spectrophotometric techniques.

14. The method according to claim 13, wherein said device is selected from the group consisting of a well, a tube, a cuvette and an apparatus which comprises a plurality of said wells, tubes or cuvettes.

15. The method according to claim 13, wherein said soluble signal is selected from the group consisting of a colored product, a chemiluminescent product, and a fluorescent product.

16. The method according to claim 13, wherein said solid support and said device are composed of the same materials.

17. A device for detecting a polynucleotide sequence according to the method of claim 1, which device comprises a solid support, having said polynucleotide sequence fixed thereto in hybridizable form.

18. A kit for detecting a polynucleotide sequence, which comprises the device of claim 17 in packaged combination with a container of an oligonucleotide or polynucleotide probe, having covalently attached thereto a chemical label comprising a signalling moiety capable of generating a soluble signal.

19. The kit of claim 18, wherein said soluble signal is a colored product or a fluorescent product.

20. The method according to claim 1 wherein part of the solid support is modified to facilitate fixing of the polynucleotide sequence to the solid support by the sequential steps of:

(a) heating or boiling the solid support in dilute nitric acid for about 45 minutes;

(b) washing or rinsing the solid support with distilled water;

(c) drying the solid support at about 115° C., for about 24 hours;

(d) incubating the solid support in contact with 10% gamma-aminopropyltriethoxysilane for about two to three hours at about 45° C.;

(e) washing with water; and

(f) drying overnight at a temperature of about 100° C.

21. The method according to claim 1 wherein part of the solid support is modified to facilitate fixation of the polynucleotide sequence to the solid support by treating the solid support with a coating of an epoxy resin.

22. The method according to claim 21 wherein part of the solid support is modified to facilitate fixation of the polynucleotide sequence to the solid support by

treating the support with the epoxy resin by the following sequential steps;

(a) applying an epoxy glue in solution with ethanol to the solid support; and,

(b) evaporating the ethanol by heating to a temperature of about 37° C. to provide a polyamine polymeric coating on the solid support.

23. The method according to claim 1 wherein said polynucleotide sequence is fixed to said solid support in double-stranded form, and denatured into single-stranded form prior to the hybridization step.

24. The method according to claim 1 wherein said polynucleotide sequence in double-stranded form is denatured, and fixed to said solid support in single-stranded form prior to the hybridization step.

25. The method according to claim 1 wherein said polynucleotide sequence to be detected is in single-stranded form and is indirectly bound to said solid support by sandwich hybridization.

26. The method according to claim 1 wherein a cell or cellular material is directly fixed to said solid support, and polynucleotide sequences within said material are hybridized to polynucleotide or oligonucleotide probes in situ.

27. The method according to claim 1 wherein said signalling moiety is a chemiluminescent agent.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
**Certificate**

Patent No. 4,994,373 Patented: February 19, 1991

On petition requesting issuance of a certificate for correction of inventorship pursuant to 35 U.S.C. 256, it has been found that the above identified patent, through error and without any deceptive intent, improperly sets forth the inventorship.

Accordingly, it is hereby certified that the correct inventorship of this patent is: Jannis G. Stavrianopolous, New York, NY (US); Dollie Kirtikar, Elmhurst, NY (US); Kenneth H. Johnston, New York, NY (US); Barbara E. Thalenfeld, New York, NY (US); and Elazar Rabbani, New York, NY (US).

Signed and Sealed this Seventeenth Day of April 2007.

WILLIAM R. DIXON, JR.
*Special Program Examiner*
Technology Center1600

## IX. EVIDENCE APPENDIX

(2) Matkovich et al. U.S. Patent No. 4,828,386

United States Patent [19]
Matkovich et al.

[11] Patent Number: 4,828,386
[45] Date of Patent: May 9, 1989

[54] MULTIWELL PLATES CONTAINING MEMBRANE INSERTS

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[73] Assignee: Pall Corporation, Glen Cove, N.Y.

[21] Appl. No.: 64,342

[22] Filed: Jun. 19, 1987

[51] Int. Cl.$^4$ .......... G01N 21/03
[52] U.S. Cl. .......... 356/246; 436/809
[58] Field of Search .......... 356/246; 436/524, 531, 436/809

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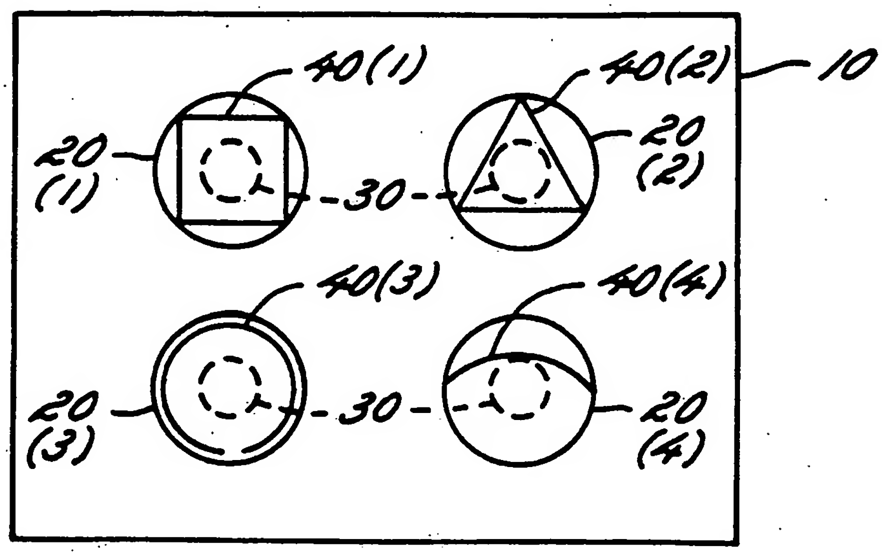
*Primary Examiner*—Vincent P. McGraw
*Attorney, Agent, or Firm*—Leydig, Voit & Mayer

[57] ABSTRACT

A multiwell plate suitable for use in a spectrometer which uses a vertical beam of light comprising a first plate having a plurality of wells for receiving sample, wherein the wells have transparent bottom surfaces to allow for the transmission of a vertical beam of light, and a unitary insert comprising a biochemically compatible microporous surface capable of binding biological materials shaped to fit into at least one well of the plate without interfering with the vertical beam of light.

20 Claims, 1 Drawing Sheet




(2)

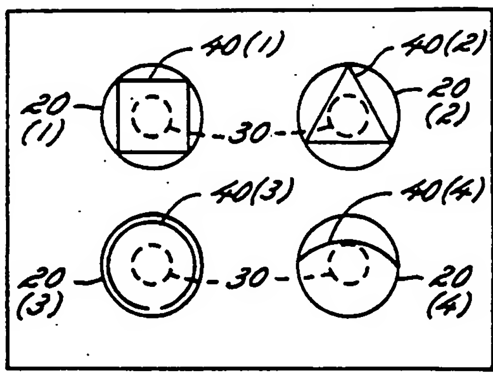



FIG. 1

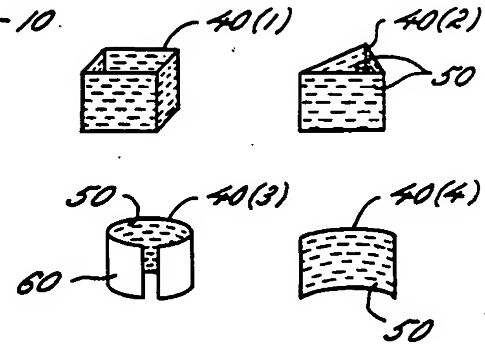



FIG. 2

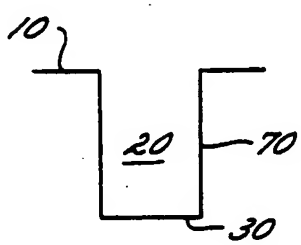



FIG. 3a

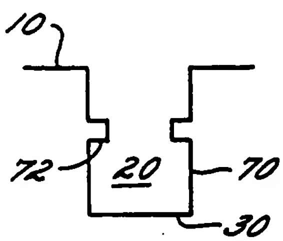



FIG. 3b

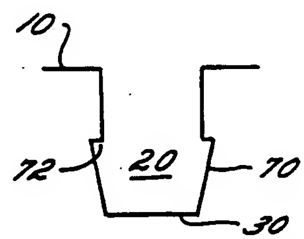



FIG. 3c

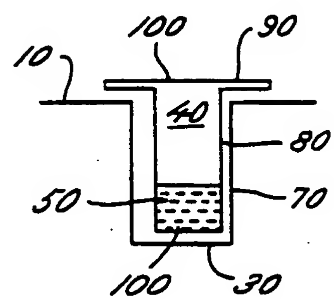



FIG. 4

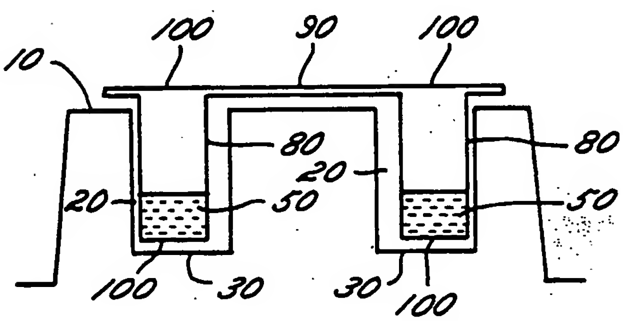
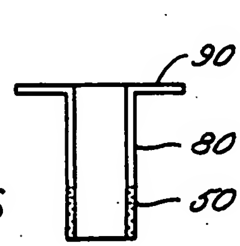



FIG. 5

FIG. 6



# MULTIWELL PLATES CONTAINING MEMBRANE INSERTS

## FIELD OF THE INVENTION

The present invention relates to multiwell plates, such as the so-called microtiter plate, particularly multiwell plates designed for use with vertical beam spectrophotometry.

## BACKGROUND

A number of diagnostic assays are carried out in automated equipment using multiwell plastic plates and automated equipment in which a vertical beam of light is used in making spectrophotometric readings in the individual wells of the plates. These plates have several common features: plastic wells with optically transparent bottom is isolated from one another with respect to liquid contained therein but physically connected in a precise geometric pattern. The wells are typically part of a plastic carrier plate, and the automated equipment is designed to have a movable stage into which one or more multiwell plates precisely fit. Most commonly these multiwell plates contain 96 wells arranged in an $8\times12$ pattern, although plates containing other numbers of wells are also available.

One common use of multiwell plates is in an automated diagnostic assay using antibodies to bind an analyte in a sample added to one or more of the wells of the plate. Before a multiwell plate can be used for this type of test, it must be coated with the appropriate antibody. This is normally accomplished by the user and consists of adding an antibody solution to the individual wells, followed by incubating and removing excess solution. During the incubation interval, the antibody binds nonconvalently to the wall and bottom of the individual wells. The amount of antibody and the tenacity of the bond that the antibody makes to the walls of the individual wells are important factors in the sensitivity and reliability of the diagnostic test that uses the multiwell plate.

When antibody-coated plates are used in an automated, vertical beam spectrophotometer, samples are added to the individual wells. The plate is then placed in the movable stage of the spectrophotometer. Activating the machine causes the stage to automatically advance into the machine, and a series of preprogrammed steps occur. In a number of machines, hollow needles descend into some or all of the wells and either inject a liquid containing reagents used in the assay or remove a liquid from a previous step. The stage then shifts sufficiently to allow the process to be repeated in the next group of wells. After the last chemical step of the sequence, which typically results in the formation of a colored product, the stage shifts to a new location so that the individual wells are placed in proper register either above or below a light source which passes a beam of light vertically through the well to a detector which measures the amount of transmitted light of a particular wavelength. This reading is converted automatically to a reading of the amount of analyte present in the sample, since the amount of color formed in the reaction is related to the amount of analyte.

The chemical and biochemical reactions that eventually result in color formation take place at the surfaces of the individual wells. Specifically, it is the surface area of the well wetted by the antibody solution initially used to coat the wells that sets the maximum level of antibody which can be bound. Since the geometry of the individual wells is essentially fixed by the constraints of the automated equipment, there is a practical limit to antibody adsorption on typical multiwell plates in current use. This can cause falsely low readings when large amounts of analyte are present, since not enough antibody will be present on the well walls to bind all of the analyte, as well as problems in sensitivity.

One attempt to overcome this limitation has employed porous latex beads contained in the wells. The antibody is bound to the latex, and the well simply becomes a chamber containing the beads.

While this approach does provide a significant increase in bound antibody, it suffers from serious practical problems. For example, the beads are typically unconstrained and can be removed accidently during the filling and emptying cycles in the automated equipment. Tests utilizing beads are therefore more sensitive to slight variations in machine fill and empty cycles than are multiwell plates that do not contain beads.

A second problem with current multiwell devices relates to the tenacity of antibody binding to well walls. Since the adsorption of antibody is basically passive (i.e., hydrophobic) in current multiwell plates, slight differences in surface characteristics from well to well can provide significant differences in the amount of antibody bound. These variations can significantly effect the reliability of diagnostic assays that utilize antibody-coated multiwell plates. Although the use of antibodies bound to latex beads avoids this problem, the latex beads are subject to the problems discussed above.

Accordingly, there remains a need for improvements in multiwell plates to provide for increased antibody binding in a more reliable manner.

## SUMMARY OF THE INVENTION

The present invention provides a multiwell plate suitable for use in a spectrophotometer which uses a vertical beam of light, comprising a first plate having a plurality of wells for receiving sample, wherein the wells have transparent bottom surfaces to allow for the transmission of the vertical beam of light, and a unitary insert comprising a biochemically compatible microporous surface capable of binding antibody shaped to fit into at least one well of the plate without interfering with the vertical beam of light.

## BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will be better understood by reference to the following detailed description when considered in combination with the figures that form part of this specification, wherein:

FIG. 1 is a plan view of a 4-well multiwell plate containing four different configurations of inserts.

FIG. 2 is a series of perspective views showing the individual inserts from the wells of FIG. 1.

FIGS. 3 (*a–c*) are a series of vertical cross-sections showing different configurations for the vertical walls of individual wells.

FIG. 4 is a cross-sectional view of a single well containing a removable insert that does not fit completely within the well.

FIG. 5 is a cross-sectional view of a multiple-projection insert in which projections fit into two adjacent wells of a multi-well plate.

FIG. 6 is a cross-sectional view of a hollow cylindrical insert.

## DESCRIPTION OF SPECIFIC EMBODIMENTS

The present invention provides a multiwell plate suitable for use in a spectrophotometer that uses a vertical beam of light but showing superior characteristics in binding antibody and other substances of biological origin. The basic multiwell plate resembles known multiwell plates in that it comprises a first plate having a plurality of wells for receiving sample affixed to or formed as part of the plate. These wells have transparent bottom surfaces to allow for the transmission of a vertical beam of light through the well and any sample that is contained therein. Superior capacity for the binding of biological substances is obtained by providing a unitary insert comprising a biochemically compatible microporous surface capable of binding antibody and/or other substances of interest for carrying out binding assays that is shaped to fit into at least one well of the plate without interfering with the vertical beam of light.

The inserts of the invention can fit either entirely within the wells of the microtiter plates or can extend above the well walls. Variations are also possible in the removability of the insert, the height of the microporous surface above the bottom of the well, the use of a backing material to support the microporous surface (the backing material being either rigid or flexible, porous or non-porous), and the composition of the microporous surface. However, the inserts are unitary; i.e., they may be inserted and/or removed from one or more wells as a unit. Accordingly, beads or other non-unitary inserts are not a part of the present invention. However, the inserts can be formed from multiple parts which are joined together to form the final unitary insert.

The configuration of the multiwell plate itself is not important to the present invention, and any of the known configurations can be used. These include unitary devices formed by an injection molding or other type of plastic-forming process. The wells can either comprise cylinders or other hollow shapes extending above the main surface of the plate that connects the wells together (the plate serving as the bottom surface of the individual wells) or the wells can comprise cylinders or other hollow shapes extending below the surface of the connecting plate, in which case the bottom surfaces of the wells can be either individually formed or formed from a lower transparent plate that interconnects the bottom surfaces of the individual wells. A number of different variations are available from commercial supply houses and can be readily adapted to form a plate of the present invention by use of the inserts described below.

The inserts of the invention will comprise at least one biochemically compatible microporous surface capable of binding antibody and other biological substances used in binding assays.

The invention can be practiced with any type of microporous binding surface (often called a reaction substrate or solid support). The phrase binding surface or reaction substrate is used here to indicate a material to which one or more of the reactants utilized in the assay is attached, whether such attachment is by a chemical bond or a physical process (such as adsorption). Although the bound material is usually an antibody or antigen, any reference herein to a binding surface capable of binding an antibody (or similar language) is not limiting or to be considered as indicating that only an antibody can be bound to the surface. Specific examples of molecules that participate in binding interactions suitable for use in assays of the type described here are set forth later in this specification. Preparation and use of solid supports per se in binding assays do not themselves constitute a part of the present invention since the preparation and use of such reaction substrates are well known. Rather, the present invention is concerned with the combination of such surfaces in particular configurations with multiwell plates that can be used in vertical beam photometry. Nevertheless, a brief description of reaction substrates is provided for completeness.

The particular material from which the binding surface is formed must not react adversely with substances found in either the samples, reagents, or solvents employed in the analyses. Preferred substrates will be formed from a liquophilic, microporous membrane or other porous material, typically having an absolute pore rating of about 0.001 to about 20 microns, preferably about 0.02 to about 8 microns, and most preferably about 0.2 to about 3 microns. The substrate preferably is also skinless. Materials which are suitable for use as the substrate also have voids volumes in the range of about 60–90%, preferably in the range of about 75–90%. Preferred materials are hydrophilic in nature and are therefore easily water-wettable and tend to freely pass and adsorb aqueous solutions. Polyamide binding surfaces are preferred. Nylon 66 is a preferred polyamide.

Liquophilicity, as used herein, refers to the wettability of the membrane by the liquid(s) with which it is contacted. The wettability or liquophilicity of a solid structure is a function of that structure's critical surface energy and the surface tension of the applied liquid. If the critical surface energy is at least as high as the surface tension of the liquid, the liquid will spontaneously wet the solid structure. For example, a microporous membrane having a critical surface energy of 72 dynes/cm or higher will be wetted by water, which has a surface tension of 72 dynes/cm; i.e., it is hydrophilic.

The capability of a porous structure (membrane or otherwise) to be wetted by a liquid can be determined by placing a drop of liquid on the porous structure. The angle of contact provides a quantitative measure of wetting. A very high angle of contact indicates poor wetting, while a zero angle of contact defines complete or perfect wetting. Materials used in the subject invention as the wettable or liquophilic porous substrate are characterized by being readily or spontaneously wetted by the applied liquid and have a low angle of contact with the applied liquid. Indeed, when a drop of a test liquid(s) is placed on a spontaneously wettable or liquophilic microporous substrate, the drop of liquid penetrates and wets the substrate, effectively providing a zero angle of contact therewith.

Wettability may also be expressed in terms of intrusion pressure which is defined as the applied pressure required for liquid to penetrate into the pores of the substrate. Materials which are particularly preferred for the substrate have intrusion pressures of or close to zero when water is the liquid.

Suitable material should also be capable of being treated with a retaining or immobilizing a substance being analyzed and/or a reactant which may be used to perform a specified test or reaction with the substance being analyzed for in a sample. The reactant, which may be of ionic, molecular, or macromolecular nature, may be immobilized on the reaction layer by strong physical forces or by being bonded in some manner, such as covalent chemical coupling, to the surface of

the reaction layer. As employed herein, the term "surface" or "surface area" refers not only to the gross surface(s) of the structure but also, in those cases where a microporous structure such as a membrane is under consideration, to the surfaces of the micropores, i.e., the interior surfaces of the structure which are contacted by fluid during use.

Materials which are preferred for the reaction substrate have large surface areas. This feature permits a greater amount or higher concentration of reactant to be immobilized in the substrate. Accordingly, higher sensitivities and/or higher capacities may be achieved.

Some of the materials which are suitable or preferred for use as the substrate in the present invention are intrinsically hydrophilic or water-wettable. Others may be modified to render them hydrophilic. For example, BIODYNE® is an N66 polyamide, microporous membrane commercially available from Pall Corporation which is inherently water-wettable by virtue of its method of manufacture (see U. S. Pat. No. 4,340,479).

Polyamides preferred for use in the present invention include nylons of the type described in U.S. Pat. No. 4,340,479, which is incorporated herein by reference. Another preferred membrane useful as the reaction layer is IMMUNODYNE™, available from Pall Corporation. IMMUNODYNE™ is a modified CARBOXYDYNE® membrane, also available from Pall Corporation. CARBOXYDYNE® is a hydrophilic, microporous, skinless nylon 66 membrane with controlled surface properties formed by the cocasting process described in U.S. Pat. application Ser. No. 850,061, as discussed below, specifically by cocasting nylon 66 and a polymer containing an abundance of carboxyl groups to form a membrane having controlled surface properties characterized by carboxyl functional groups at its surfaces. IMMUNODYNE™ membranes may be prepared from CARBOXYDYNE® membranes by treating them with trichloro-s-triazine in the manner described in U.S. patent application Ser. No. 642,899, discussed below.

Also included among the preferred polyamide membranes for the present invention are hydrophilic, microporous, skinless polyamide membranes with controlled surface properties of the type described in (1) U.S. patent application Ser. No. 850,061, filed Apr. 7, 1986, which is a continuation application of U.S. patent application Ser. No. 459,956, filed Jan. 21, 1983, which in turn is a continuation-in-part application of U.S. patent application Ser. No. 346,118, filed Feb. 5, 1982, and in (2) U.S. patent application Ser. No. 848,911, filed Apr. 7, 1986, which is a continuation application of U.S. patent application Ser. No. 460,019, filed Jan. 2, 1983, which is a continuation-in-part application of U.S. patent. application Ser. No. 346,119, filed Feb. 5, 1982.

All of the aforementioned U.S. patent applications are specifically incorporated herein by reference. These hydrophilic, microporous, substantially alcohol-insoluble polyamide membranes with controlled surface properties are formed by cocasting an alcoholinsoluble polyamide resin with a water-soluble, membrane-surface-modifying polymer having functional polar groups. Like the preferred hydrophilic, microporous nylon membranes which do not have controlled surfacemodified polar groups present, the polyamide membranes having controlled surface properties are also skinless; that is, they are characterized by through pores extending from surface-to-surface which are of substantially uniform size and shape. If desired, however, materials having tapered through pores, i.e., pores which are larger at one surface of the sheet, narrowing as they approach the opposite surface of the sheet, may be used.

The surface-modifying polymers used to prepare the polyamide membranes with controlled surface properties comprise polymers which contain substantial proportions of chemical functional groups, such as hydroxyl, carboxyl, amine, and imine groups. As a result, the membranes include, at their surfaces, high concentrations of functional groups such as hydroxyl, carboxyl, imine, or a combination of any of the above groups which do not react with one another. These polyamide membranes having controlled surface properties have higher concentrations of carboxyl or imine groups at their surfaces than the preferred microporous, hydrophilic, skinless polyamide membranes described above which do not have controlled surface properties, i.e., those which are formed from the preferred polyamide resin but are not cocast with surface-modifying polymer.

The substrate may be treated by any method known to one of skill in the art to deposit and/or bind reagents thereto. Treatment of the substrate with a suitable reagent(s) may be performed at the time at which diagnostic tests are to be performed, including addition of the test reagent(s) both immediately preceding and following introduction of the sample containing the analyte, or the substrate can be pretreated with at least one test reagent. Typically, pretreatment is conducted after the substrate has been prepared but before the device is shipped to a user.

A useful method of binding reagents of a molecular nature, especially macromolecules, and particularly those of a biological nature, is disclosed in U.S. patent application Ser. No. 642,899, filed Aug. 21, 1984, and specifically incorporated herein by reference. This application describes a method for immobilizing a wise range of biologically active substances on active nylon surfaces. In the application the reagent bound to the surface is referred to as an acceptor. The acceptor-bound surfaces described in the application are capable of immobilizing and binding a wide variety of biologically-active compounds, specifically ligands, to the acceptor molecules. Using such reaction layers permits the testing of bodily fluids, such as blood, serum, plasma, urine, saliva, and the like, and testing for particular substances by chemical assays or immunosassays that use a fluoroescent label. The macromolecules used as reagents and bound to the substrate or which are assayed for using the device of the present invention generally include materials of a biological nature and are frequently proteinaceous in nature. The reagent or acceptor molecule bound directly to the reaction substrate or the ligand being tested for include such substances as immunoglobulins or antibodies, either polyclonal or monoclonal, antigenic substances, apoproteins, receptors, glycoproteins, lectins, carbohydrates, hormones, enzymes, carrier proteins, heparin, coagulation factors, enzyme substrates, inhibitors, cofactors, nucleic acids, etc.

The microporous reaction surface can be utilized by itself, be applied to a rigid or flexible backing to form a layered insert, or be attached to or form part of a larger insert. Preferred backing are prepared from the same basic material as the microporous reaction/binding surface in order to provide compatible materials for attaching together. For example, a solid nylon backing can be provided for a microporous nylon surface. However,

any combination of materials can be used as long as the attaching process does not adversely affect the binding properties of the microporous surface to an unacceptable degree.

Whether the microporous surface forms the entire insert or only part thereof, it is preferred that the microporous surface of the insert reside, when in use, in a lower portion of the multiwell plate well in order that the microporous surface is immersed completely within the liquid reaction medium. If a microporous surface extends above the liquid surface, capillary action within the pores will tend to draw reaction fluids into the portion of the microporous surface above the liquid surface. Removal of the liquid reaction medium followed by addition of a second medium will typically result in further wicking of the second liquid. For example, if the second liquid is a wash solution, rather than washing out the first liquid wicked into the upper portion of the microporous surface, the washed solution will merely push the first liquid higher or, if capillarity is exhausted, will not affect the liquid retained in the upper portion of the microporous surface. Accordingly, it is preferred that the microporous surface extend in the well no higher than the maximum height intended for liquid. This maximum vertical height is typically less than two-thirds, preferably less than one-half, and most preferably less than one-quarter of the height of the vertical walls of the well. If a microporous insert of the type that fits entirely within the well is utilized, the insert can reside on the bottom surface of the well and extend upward to the heights indicated above. If the microporous surface is part of a larger insert that fits only partly within the well, it is preferred that the microporous surface be on the lower portion of the insert so that it resides within the lower portion of the well as described above.

A principal characteristic of an insert of the invention is that it is shaped to fit into the well without interfering with the vertical beam of light from a vertical beam spectrophotometer or that it is easily removable to avoid interferring with the light beam during the measurement step. This beam of light typically passes through the center of the well. Accordingly, configurations for inserts that maintain all surfaces outside the central portion of the well are preferred. Typically, the vertical beam of light has a diameter less than one-half, preferably less than one-quarter, of the diameter of the well and is centered on the well. Accordingly, the unitary insert should be shaped so as to avoid interfering with this portion of the center of the well. However, it is interference with transmission of light, particularly light of the wavelength being measured, that is important, and some embodiments of the invention comprise transparent supports, connecting pieces, and the like (such as the top or bottom of a closed cylinder) that traverse this central portion of the reaction well. However, preferred embodiments of the invention do not interfere in any manner with the central portion of the well.

The geometry of the insert can be varied significantly and still fall within the scope of the present invention. For example, a rectangular sheet of microporous material slightly longer than the diameter of the well can be inserted fully into the well. If the microporous material is flexible and resilient, or is backed by a resilient material, the two ends of the insert will press against the vertical walls of the well and will slightly bow the sheet of microporous material. This bowing action removes the sheet from the center of the well. If the length of the microporous material is increased so that it is substantially equal in length to the circumference of the well, the sheet can be formed into the shape of an open cylinder and inserted into the well, where the sheet will fit against the vertical walls of the well. Providing a flexible and resilient microporous material (or microporous material affixed to a flexible and resilient backing) will result in a snug fit in the well as the cylinder tries to expand to its original flat shape.

In addition to curved inserts as discussed above, it is also possible to form flat sheets of microporous material into hollow polyhedrons without a top or bottom surface. For example, three sheets or a continuous folded surface of microporous material can be formed into the shape of a hollow prism or four sheets or a continuous folded surface of microporous material can be formed in the shape of a hollow cube. The sides of the polyhedrons are selected so that the corners of the inserts just touch the vertical walls of the well. Accordingly, light passes undisturbed through the central portion of the well.

By sizing the insert as described above, the resiliency of the insert material can be used to ensure a tight fit within the individual wells. A tight fit is useful in preventing accidental dislodging of the insert during shipping and handling. Thus, the inserts can be used in standard microtiter plates having smooth, substantially vertical walls. However, it is also possible to adapt microtiter plates specifically for use with inserts as described above by providing one or more inward projection in the inner surface of the well. An insert is used having a vertical height less than the vertical height of the well walls and the inward projection is placed just above the height of the insert, whereby the insert is locked into position when fully inserted into the well. A number of different types of projections can be used depending on the configuration of the insert. For example, if a cylindrical insert is used, a single small inward projection or a small number of small inward projections can be used to keep the cylinder in place. Such inward projections would only cover a small fraction of the inside circumference of the well wall and would be discontinuous. However, if a sheet only slightly longer in diameter than the diameter of the well is used (having only two contact points at the well walls) or a hollow polyhedron as described above is used (having three contact points for a prism, four contact points for a cube, etc.), it is preferred to utilize a continuous inward projection, such as a continuous ridge or ring, in order to avoid the problem of correctly registering the contact points with the inward projections.

In an alternative embodiment of the invention, an insert that does not fit completely within the well can be utilized. Inserts that project above the well walls are particularly suitable for applications in which the inserts are removed at various stages of processing the multiwell plate. Such inserts can either fit into individual wells or can be attached to one another so that they may be inserted into a plurality of wells at the same time. The connection between the various portions of the insert that fit into the individual wells is immaterial to the practice of the invention. However, most inserts will comprise an insert plate in which projections are formed. The insert plate will comprise one or more projections that fit into one or more of the wells of the multiwell plate. A preferred form for the projection is a hollow cylinder with open top and bottom surfaces,

with the open cylinder projecting downward into the well from the insert plate. However, cylindrical inserts with closed tops and/or bottoms can also be used if the top and bottom surfaces transmit the beam of light either substantially without loss or with equal loss through all top and bottom surfaces (so that an equal change occurs in light transmitted in all wells, including control wells in which no reaction takes place). Projections with closed bottom surfaces in which the walls of the projection are nonporous and a microporous material is placed on the outer surface of the projection in the lower portion of the well offer the advantage of utilizing smaller volumes of liquid since liquid will be displaced upwardly by the projection as it is inserted into the well. Accordingly, fluid will surround and closely contact the microporous surface on the lower outer portion of the projection, and it will not be necessary to fill the well with a large volume of reagent liquid.

Although multiple, interconnected inserts which are removable can be used and then removed prior to transmission of light, it is also possible to lock the insert to the multiwell plate. Numerous methods for locking two contacting devices to each other are known in the art and need not be discussed here in detail. Examples include press fit connections, adhesives, spring clips, bolts, and the like. Preferred are locking devices which automatically engage when the projections are fully inserted into the wells.

Turning now to the figures, FIG. 1 is a plan view of a 4-well multiwell plate showing four different geometric arrangements of inserts. Four individual wells, indicated as 20(1) through 20(4) are seen in interconnecting horizontal plate 10. In this view from above, the bottom (30) of each well is seen. The vertical light beam location is indicated by the dashed circle surrounding the number 30. Four inserts (40) are seen in the individual wells, each insert being numbered 40(1) through 40(4) corresponding to the numbering system utilized for the individual wells.

Well 20(1) contains insert 40(1), which is in the shape of a hollow cube lacking top and bottom surfaces. The sides of insert 40 are selected so that each corner of the cube touches or closely approaches the inner vertical wall of well 20(1). A similar situation is seen in well 20(2), except that insert 40(2) is in the shape of a hollow prism lacking top and bottom surfaces.

Well 20(3) contains insert 40(3) in the shape of a sheet approximately equal in length to the circumference of well 20(3). Insert sheet 40(3) is therefore formed into the shape of a cylinder that fits tightly against the walls of well 20(3). In this embodiment, insert 40(3) is formed in two parts from layers of microporous material 50 and a resilient backing 60. The springiness of the resilient backing provides the force by which insert 40(3) is retained firmly within the well as it tries to spring back to its original flat shape.

Well 20(4) contains insert 40(4), which comprises a sheet of microporous surface material slightly longer than the diameter of well 20(4). The flexure of the sheet moves the central portion of the sheet away from the central portion of well 20(4), thereby allowing the light beam to pass undisturbed through well bottom 30. This embodiment requires that the microporous surface be either resilient or rigid or that the microporous surface be attached to a rigid or resilient backing material.

FIG. 2 is a series of perspective drawings of the inserts shown in FIG. 1. Insert 40(1) is in the form of a hollow cube lacking a top or bottom surface and comprises a microporous surface material without a backing. A similar configuration is seen for insert 40(2), except that the insert is in the form of a hollow prism rather than a hollow cube. Insert 40(3) is in the form of a hollow cylinder that fits just within the interior walls of the sample well. A resilient backing 60 provides springiness to hold the cylinder in place while the microporous surface 50 faces the interior of the well and provides a reaction surface. Insert 40(4) is a slightly arched sheet.

FIG. 3 is a series of vertical cross-sectional views showing microtiter plate wells. Well 20 has a transparent bottom surface 30 which is attached through continuous vertical walls 70 to plate 10 which interconnects the plurality of sample wells (not shown). In FIG. 3A, vertical walls 70 are smooth and continuous. In the embodiment shown, walls 70 are exactly vertical. It is possible to have these walls be merely substantially vertical; for example, the diameter of the well at the top of the well can be slightly greater than or slightly less than the diameter at the bottom of the well. FIG. 3B shows a well 20 with a bottom 30 and vertical walls 70 connected to horizontal plate 10. An inward projection 72 in the form of a raised ring around the inner circumference of the well 20 is present in well 70. In this vertical cross-section, the inwardly projecting ring can be seen at two locations opposite each other. The height of the inward projection above the bottom surface 30 of the well is selected to be slightly larger than the height of an insert of the type shown in FIG. 2. Inwardly projecting ring 72 thus acts as a retaining ring. As shown in FIG. 3C, inward projection 72 need not be a raised ring or other raised projection in vertical wall 70 but may represent a narrowing of the diameter of well 20 near the top of the wall.

FIG. 4 shows a removable insert that does not fit completely within well 20. In the embodiment shown, insert 40 comprises a horizontal plate 90 that fits over plate 10 in which well 20 is formed. A projection 80 extends below plate 90 into the lower region of well 20 near bottom surface 30. A microporous surface 50 is present on the lower portion of projection 80 in the region of well 20 in which liquid will be present. The embodiment shown has upper and lower surfaces 100 of insert 40, which may or may not transmit light. In embodiments in which upper and lower surfaces 100 do not transmit light or transmit light altered by passage through the surfaces, the insert can be removed prior to reading the transmission of light through the reaction fluid in well 20. By providing the insert in a removable form, it is considered to be shaped to fit the well without interfering with passage of a vertical beam of light. However, insert 40 can be manufactured from a transparent material so that upper and lower surfaces 100 transmit light substantially unchanged, in which case there is no need to remove the insert prior to reading transmittance.

FIG. 5 shows an embodiment of the invention similar to that present in FIG. 4 but in which a plurality of projections 80 are connected by a horizontal plate 90. Each of the projections 80 extends into one of the wells 20 that are formed in plate 10. As in FIG. 4, projections 80 contain a lower portion having a microporous surface 50. FIG. 5, in contrast to FIGS. 3 and 4 which showed only the region of plate 10 adjacent to well 20, shows a complete cross-section of plate 10 including

vertical extensions 12 that extend downward from horizontal plate 10 to form the base on which the plate rests.

FIG. 6 is a vertical cross-section of an insert of the invention in which projection 80 is in the form of a hollow cylinder attached to plate 90. The lower portion of projection 80 is either formed from hydroporous material 50 or has hydroporous material 50 coated on its surface. The insert shown in FIG. 6 is similar to the insert shown in FIG. 4 but does not have upper or lower surfaces through which light passes. Hollow cylinders can also be prepared in multiple cylindrical inserts joined by a plate in analogy to FIG. 5.

All publications and patent applications mentioned in this specification are indicative of the level of skill of those skilled in the art to which this invention pertains. All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

The invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the appended claims.

What is claimed is:

1. A multiwell plate suitable for use in a spectrophotometer which uses a vertical beam of light comprising:
- a first plate having a plurality of wells for receiving sample, wherein said wells have transparent bottom surfaces to allow for the transmission of a vertical beam of light;
- a unitary insert comprising a biochemically compatible microporous binding surface shaped to fit into at least one well of said plate without interfering with said vertical beam of light so as to provide a free light path through said well, said free light path passing through said sample when said sample is present in said well.

2. The multiwell plate of claim 1, wherein said insert comprises a second plate arranged to fit over said first plate and having one or more projections which fit into said one or more of said wells.

3. The multiwell plate of claim 2, wherein said projections comprise hollow cylinders with open top and bottom surfaces.

4. The multiwell plate of claim 2, wherein said projections comprise cylinders with a top or bottom surface through which said beam of light is transmitted substantially without loss.

5. The multiwell plate of claim 2, wherein said insert is removable.

6. The multiwell plate of claim 2, wherein said second plate locks to said first plate when said projection is fully inserted into said well.

7. The multiwell plate of claim 2, wherein said insert comprises a sufficient number of projections to fit into all of said wells.

8. The multiwell plate of claim 2, wherein said insert comprises a single projection which fits into a single well.

9. The multiwell plate of claim 1, wherein said insert fits completely within said well.

10. The multiwell plate of claim 9, wherein said insert comprises a sheet of microporous material longer than the diameter of said well.

11. The multiwell plate of claim 10, wherein said sheet is substantially equal in length to the circumference of said well and said sheet fits against the vertical walls of said well.

12. The multiwell plate of claim 9, wherein said insert comprises a hollow polyhedron without a top or bottom surface.

13. The multiwell plate of claim 12, wherein said polyhedron is a triangular prism.

14. The multiwell plate of claim 9 wherein said insert fits within the bottom two-thirds of said well.

15. The multiwell plate of claim 14, wherein said well comprises substantially vertical walls and said vertical walls comprise an inward projection above the height of said insert, whereby said insert is locked into position in said well.

16. The multiwell plate of claim 9, wherein said microporous surface comprises polyamide affixed to a flexible backing sheet.

17. The multiwell plate of claim 16, wherein said backing sheet is resilient.

18. The multiwell plate of claim 9, wherein said insert is irremovably attached to said well.

19. The multiwell plate of claim 9, wherein said insert is removably located within said well.

20. The multiwell plate of claim 1, wherein said microporous surface comprises polyamide.

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## IX. EVIDENCE APPENDIX

(3) Dawson et al., Analytical Biochemistry 341 (2005) 352-360

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Analytical Biochemistry 341 (2005) 352–360

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# Spotting optimization for oligo microarrays on aldehyde–glass

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Received 2 February 2005

Available online 13 April 2005

**Abstract**

Low-density microarrays that utilize short oligos (<100 nt) for capture are highly attractive for use in diagnostic applications, yet these experiments require strict quality control and meticulous reproducibility. However, a survey of current literature indicates vast inconsistencies in the spotting and processing procedures. In this study, spotting and processing protocols were optimized for aldehyde-functionalized glass substrates. Figures of merit were developed for quantitative comparison of spot quality and reproducibility. Experimental variables examined included oligo concentration in the spotting buffer, composition of the spotting buffer, postspotting "curing" conditions, and postspotting wash conditions. Optimized conditions included the use of 3–4 μM oligo in a 3× standard saline citrate/0.05% sodium dodecyl sulfate/0.001% (3-[(3-cholamidopropyl) dimethylammonia]-1-propane sulfonate) spotting buffer, 24-h postspotting reaction at 100% relative humidity, and a four-step wash procedure. Evaluation of six types of aldehyde-functionalized glass substrates indicated that those manufactured by CEL Associates, Inc. yield the highest oligo coverage.
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*Keywords:* Low-density microarrays; Diagnostics; Spotting solution; Aldehyde substrates; Reproducibility

Microarray technology is extremely powerful for massively parallel differential gene expression analyses [1] in which relatively long cDNA fragments (>100 nt) are immobilized on a substrate and exposed to cDNAs that derive from mRNA. These cDNAs are made from "treated" and "untreated" states that are differentially fluorophore-labeled. The ratio of the two fluorescence signals serves as a measure of changes in mRNA levels. Many experimental and technological challenges must be addressed to make the data generated from these experiments more reproducible [2–7]. As many reviews and publications have outlined [8–17], the most pressing difficulties in obtaining reliable data for these multiplex analyses lie in the areas of sequence selection [12–17] and methods of data analysis [8–11]. DNA microarrays are also increasingly attractive for diagnosis as research directed at diagnostic applications is rapidly expanding and ranges from microbiology to clinical virology [18–21]. The oligonucleotide microarrays used for diagnostic applications tend to be lower in density and employ short oligos [20–22]. Here we define "short" oligonucleotides to be those up to 100 nucleotides in length, which can be synthesized using standard phosphoramidite chemistry and/or purchased commercially.

A number of noncovalent and covalent chemistries can be used to immobilize oligos on a glass substrate [22]. Noncovalent immobilization (including the use of polylysine-coated and aminopropylsilane-coated slides) is commonly used for gene expression microarrays, whereas a single terminal covalent attachment is preferred for short oligonucleotides. This terminal covalent attachment allows the entire oligonucleotide to be available for hybridization and to withstand the high temperatures and salt concentrations often required during the stringent washing conditions in subsequent steps of microarray processing. Direct covalent coupling is most commonly achieved using amino-terminated oligos and *

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0003-2697/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.ab.2005.03.029

## X. RELATED PROCEEDINGS APPENDIX

(1) Memorandum Opinion on Claim Construction, Oxford Gene Technology Ltd. v. Affymetrix, Inc., Civil Action No. 99-348-JJF before the United States District Court for the District of Delaware, November 5, 2000.

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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|---|---|---|
| OXFORD GENE TECHNOLOGY LTD., | : | |
| Plaintiff, | : | |
| v. | : | Civil Action No. 99-348-JJF |
| AFFYMETRIX, INC., | : | |
| Defendant. | : | |

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Attorneys for Defendant.

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**MEMORANDUM OPINION**

November 5, 2000
Wilmington, Delaware

Joseph J. Farnan Jr.

**FARNAN, District Judge.**

Presently before the Court are issues of claim construction presented by the parties.

**1. Claim 1 - "segregating"**

In offering its construction of this claim language, Oxford Gene Technologies Ltd. ("OGT") expresses its concern that Affymetrix Inc. ("Affymetrix") uses the "segregating" term to inject a "physical barriers" limitation in the claim. (D.I. 237, p. 13). Affymetrix answers this charge by asserting that:

> OGT misconstrues Affymetrix' position with regard to the term "segregating" as <u>requiring</u> a barrier. Affymetrix' construction does not require a specific physical barrier, rather it requires something to interact with the support to confine the claimed nucleotide precursor, a liquid. A barrier is an example of this, as shown in Figure 3. Something else which interacts with the support may suffice, perhaps a channel or microtiter well, although what that other thing may be is not suggested by the specification.

(D.I. 242, pp. 11,12).

It is this position, combined with Affymetrix' view that "the segregating step must be directed to a liquid since each have the common denominator of the discrete cell locations" (<u>Id.</u> at p. 14) that is at the heart of the dispute between the parties. Affymetrix construes "segregating" to require an action with a liquid on the support material. Specifically, Affymetrix requests the Court to construe the term to require "applying something to the support material to confine a reagent." (<u>Id.</u> at p. 6). OGT's construction requires the performance, either conceptually or physically, of an identification of a distinct or

distinguishable area or region on the support material.

The Court will resolve this dispute by construing the term "segregating" in accordance with its plain and ordinary meaning as it would be understood by one skilled in the art.

The Court construes the "segregating" term not to be restricted by the requirement of some act with a liquid on the support material. The Court interprets the term to advise the public that areas or regions of the support material must be identified or distinguished from the entire surface so as to permit, in subsequent steps of the method, an area that has been previously identified to be a location where "coupling" will occur.

Thus, the Court construes the term "segregating" to mean identifying or distinguishing regions or locations on the support material (where the oligonucleotides of the array will be synthesized).

**2. Claim 1 - "support material"**

In construing the term "support material" the Court has considered the term's plain and ordinary meaning, the patent specification and the prosecution history.

Based upon a review of these sources, the Court construes "support material" to mean a solid material with a mostly flat surface, to which an oligonucleotide can be attached.

**3. Claim 1 - "discrete cell locations"**

In construing the term "discrete cell locations" the Court

has considered the plain and ordinary meaning of the term discrete as it may be applied in the context of Claim 1. The Court has further relied upon the specification, including Example 3, and the relevant portions of the prosecution history identified by the parties in their papers and arguments.

The Court construes "discrete cell locations" to mean separate, distinct regions of the support material.

**4. Claim 1 - "nucleotide precursor"**

A review of the papers submitted and argument of counsel leads the Court to conclude that no relevant dispute exists concerning this term, and that the term should be interpreted by its plain and ordinary meaning.

**5. Claim 1 - "continuing the sequence of coupling steps"**

A review of the papers submitted and argument of counsel leads the Court to conclude that no relevant dispute exists concerning this term, and that the term should be interpreted by its plain and ordinary meaning.

**6. Claim 4 - "means for coupling said nucleotide precursors"**

The Court agrees with OGT that this is a means-plus-function claim element that permits the recited function to be performed by any of the recited means. Upon consideration of the patent claims the Court construes this means-plus-function claim to permit the function to be performed by a mask, a laser typesetter, an ink-jet printer, computer-controlled printing device, or their equivalents. Unless there is some critical need

for an instruction to the jury, the Court does not intend to interpret the claim in its claim construction order.

**7. Claim 5 - "mask"**

For the reasons discussed above concerning Claim 4 the Court will not construe the claim term "mask" in its claim construction order.

**8. Claim 7 - "a polynucleotide"**

The Court has considered the papers submitted by the parties and the argument of counsel concerning the term "a polynucleotide." In addition to "a polynucleotide," the parties have asserted different interpretations of other terms in Claim 7, among which are the terms: "randomly degrading," "mixture," "the mixture being labeled to form labeled material," "having been synthesized in situ," and "a covalent linkage." The Court's view is that the only term that may require construction beyond its plain and ordinary meaning as understood by one skilled in the art is the term "a polynucleotide."

Unless one of the parties can convince the Court of some legal reason why it should construe the other terms presented as disputed, the Court will limit its construction to the term "a polynucleotide."

After considering the intrinsic evidence offered by the parties, the Court construes the term "a polynucleotide" to mean one or more polynucleotides.

The Court reaches this conclusion based on the legal

principle that use of the modifier "a" does not necessarily limit the term modified by "a" to one, but, in the context of the intrinsic evidence offered, may certainly be construed to mean one or more. In this regard, the Court finds nothing in the patent itself, the specification or the prosecution history that limits the term "a polynucleotide" to mean one polynucleotide and, when considered in the overall context of the invention of the '637 patent, the Court is persuaded that the term should be construed to mean "one or more" polynucleotides.

Thus, the Court construes the term "a polynucleotide" in Claim 7 to mean one or more polynucleotides.

An order will be entered setting forth the claim construction discussed in this memorandum opinion.

## X. RELATED PROCEEDINGS APPENDIX

(2) Order on Claim Construction, Oxford Gene Technology Ltd. v. Affymetrix, Inc., Civil Action No. 99-348-JJF before the United States District Court for the District of Delaware, November 5, 2000.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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|---|---|---|
| OXFORD GENE TECHNOLOGY LTD., Plaintiff, | : | |
| v. | : | Civil Action No. 99-348-JJF |
| AFFYMETRIX, INC., Defendant. | : | |

**ORDER**

The parties have presented several issues of claim construction which require the Court to construe certain language of the '637 patent-in-suit. In performing this task, the Court has considered the intrinsic evidence of record, i.e., the patent itself, including the claims, the specification, the prosecution history as admitted into evidence, the claim construction briefs of the parties (D.I. 237 and D.I. 242) and the October 30, 2000 oral argument of counsel. Further, the Court has discussed its decisions on the disputed terms in a Memorandum Opinion issued this date.

NOW THEREFORE, IT IS HEREBY ORDERED that the following claim terms of United States Patent Number 5,700,637 are construed to have the meanings indicated:

1. Claim 1 - "segregating"

The term "segregating" means identifying or distinguishing regions or locations on the support material.

(2)

2. Claim 1 - "support material"

The term "support material" means a solid material with a mostly flat surface, to which an oligonucleotide can be attached.

3. Claim 1 - "discrete cell locations"

The term "discrete cell locations" means separate, distinct regions of the support material.

4. Claim 4 - "means for coupling said nucleotide precursors"

The Court declines to interpret this term, but has set forth its understanding of the means-plus-function analysis of this Claim.

5. Claim 7 - "a polynucleotide"

The term "a polynucleotide" means one or more polynucleotides.

11-5-00
DATE

Joseph J. Farnan Jr.
UNITED STATES DISTRICT JUDGE

## X. RELATED PROCEEDINGS APPENDIX

(3) Memorandum Opinion and Order on Claim Construction, Oxford Gene Technology Ltd. v. Mergen Ltd., et al., Civil Action No. 02-1695-KAJ before the United States District Court for the District of Delaware, 2004 WL 2211971, September 29, 2004.

H Oxford Gene Technology Ltd. v. Mergen Ltd.
D.Del.,2004.
Only the Westlaw citation is currently available.
United States District Court,D. Delaware.
OXFORD GENE TECHNOLOGY LIMITED, Plaintiff,
v.
MERGEN LTD., et al., Defendants.
**No. 02-1695-KAJ.**

Sept. 29, 2004.

Richard K. Herrmann, Blank Rome LLP, Wilmington, Delaware, for plaintiff.
Mark A. Pals, Imron T. Aly, Bryan S. Hales, and Stephen T. Webb, Kirkland & Ellis LLP, Chicago, Illinois, of counsel.
Philip A. Rovner, Potter Anderson & Corroon LLP, Wilmington, Delaware, for defendant.
Paul J. Andre, Lisa Kobialka, and Ulysses S.T. Hui, Perkins Coie LLP, Menlo Park, California, of counsel.

MEMORANDUM OPINION

JORDAN, J.

I. INTRODUCTION

*1 This is a patent infringement case. Before me are the parties' requests for construction of the disputed claim language of U.S. Patent No. 6,054,270 (issued April 25, 2000)("the '270 patent"), pursuant to *Markman v. Westview Instruments, Inc.*, 52 F.3d 967 (Fed.Cir.1995) (en banc), *aff'd*, 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996). Plaintiff in this case is Oxford Gene Technology Ltd. ("OGT"). The defendant is Mergen Ltd. ("Mergen"). The parties have fully briefed and argued their positions. Jurisdiction is proper under 28 U.S.C. § 1338.

II. BACKGROUND

A. Procedural Background

OGT filed a complaint for patent infringement against defendant Mergen on December 23, 2002.[FN1] (Docket Item ["D.I."] 1.) Mergen filed a counterclaim against OGT on February 19, 2003. (D.I.25.) OGT and Mergen are scheduled to try this case to a jury beginning on February 7, 2005.

FN1. Originally, OGT filed a complaint against Mergen; Clontech Laboratories, Inc., doing business as BD Biosciences Clontech; Genomic Solutions Inc.; PerkinElmer Life Sciences, Inc.; Axon Instruments, Inc.; and BioDiscovery, Inc. (D.I.1.) OGT having settled with the others, the only remaining defendant in this dispute is Mergen.

B. The Disclosed Technology

The '270 patent discloses technology related to the making and using of microarrays in the study of DNA (deoxyribonucleic acid) and RNA (ribonulceic acid). See '270 patent, col. 1, ll. 30-48.

1. DNA and the Genetic Code

Genes, which provide the basic information for the operation of living organisms, are made up of DNA. (D.I. 174 at 1; D.I. 175 at 4.) Human genes act as the blueprint (the genetic code) for proteins involved in the function or structure of the human body. (*Id.*) DNA is a chain or strand comprising various combinations of four different nucleotides. (*Id.*) Each of the four nucleotides consists of a phosphate, a sugar (deoxyribose), and an organic base. (D.I. 175 at 4.) There are four different organic bases: adenine ("A"), cytosine ("C"), guanine ("G"), and thymidine ("T.") [FN2] (D.I. 174 at 1; D.I. 175 at 4.) Any one of these organic bases can be a component of a nucleotide. (D.I. 174 at 1; D.I. 175 at 4.) A nucleotide is distinguished by the organic base it contains. (D.I. 174 at 1.) The particular sequence of nucleotides in a strand of DNA determines what proteins will be made for the carrying out of functions in the human body. (*See* D.I. 174 at 1-2; D.I. 175 at 5.) DNA containing two or more nucleotides is referred to as a "polynucleotide." (*See* D.I. 175 at 4.) Usually, however, shorter polynucleotides are referred to as "oligonucleotides." (*See* D.I. 175 at 4.)

FN2. In an RNA nucleotide, there are also four different organic bases. They include the first three listed above and uridine, which replaces thymidine. (D.I. 175 at 4, n. 2). The sugar in an RNA molecule is ribose rather than deoxyribose.

(3)

(Id.)

When two strands of DNA are brought together under particular conditions, interactions may occur to hybridize, or bind the two strands together. (D.I. 174 at 2; D.I. 175 at 5.) Hybridization can only occur between complementary bases. (Id.) A is complementary to T, so A can only bond with T and vice versa. (Id.) C is complementary to G, so C can only bond with G and vice versa. (Id.) This is also referred to as "base-pairing." (D.I. 174 at 2.) When two complementary strands of DNA hybridize, they form the now famous double-helix structure. (Id.) Two perfectly complementary sequences of DNA will form the strongest bonds and be the most stable when hybridized. (D.I. 174 at 2; D.I. 175 at 5.) Two DNA sequences that are not perfect complements may still hybridize, but bonds will only form between bases that are matched with their complements. (Id.) Thus hybridization between two DNA sequences that are not perfect complements is less stable.[FN3](Id.)

FN3. A DNA sequence of AAAA will be more stable when hybridized with its perfect complement, TTTT, than with a sequence such as TTCT, which is not a perfect complement. This is because the third A will not form a bond with the C in the latter sequence. (*See* D.I. 174 at 2; D.I. 175 at 5.)

*2 The process of hybridization is used as a tool to learn information about a sample of DNA. (D.I. 174 at 2; D.I. 175 at 6.) In a typical experiment, a known sample of DNA is placed near an unknown sample of DNA under particular conditions to promote hybridization. (Id.) The conditions can be controlled such that perfect complements can hybridize, but imperfect complements cannot. (D.I. 175 at 6.) The interaction of the complements thus provides useful information about the unknown sample of DNA.[FN4]This technique has utility in a variety of applications, including the detection of genetic disorders where mutations may alter the base sequence in a strand of DNA. (*See* id.)

FN4. If hybridization occurs, the unknown sample's sequence is learned. If hybridization does not occur, the complement to the known sample is ruled out as a possible sequence for the unknown. (*See* D.I. 174 at 2-3; D.I. 175 at 6.)

2. The '270 Patent

The '270 patent discloses methods of making and using arrays of oligonucleotides. (D.I. 174 at 3.) Oligonucleotides of known sequence, called probes, are immobilized by attaching them to particular locations on a solid material forming an array. (D.I. 174 at 3; D.I. 175 at 7.) For a given experiment, an unknown sample, referred to as a polynucleotide, is applied to the oligonucleotide array. (D.I. 174 at 4; D.I. 175 at 7.) Under suitable conditions, the unknown polynucleotide may hybridize with one or more of the oligonucleotide probes, and information may thereby be gained regarding the unknown polynucleotide's sequence.[FN5](Id.)

FN5. The unknown polynucleotide may be labeled in order to observe its hybridization with an oligonucleotide probe. (D.I. 175 at 7.)

There are two basic methods of making arrays of oligonucleotides. (D.I. 174 at 4.) One method is referred to as "*in situ* synthesis," which "refers to the process of chemically building the oligonucleotides from smaller units *on the array* where they will be used."(Id. (emphasis added).) *In situ* synthesis is also referred to as monomer-by-monomer oligonucleotide synthesis. The other method, called "deposition," refers to the process of "synthesizing the oligonucleotides *off of the array* and then attaching (depositing) the oligonucleotides to known locations on the array."(Id. (emphasis added).) Either method results in oligonucleotide probes of known sequence, at known regions of an array. (Id.) Based on the type of experiment desired, a variety of arrays can be constructed. (Id. at 4-5.)

III. APPLICABLE LAW

Patent claims are construed as a matter of law. *Markman,* 52 F .3d at 979. A court's objective is to determine the plain meaning, if any, that those of ordinary skill in the art would apply to the language used in the patent claims. *Waner v. Ford Motor Co.,* 331 F.3d 851, 854 (Fed.Cir.2003) (citing *Rexnord Corp. v. Laitram Corp.,* 274 F.3d 1336, 1342 (Fed.Cir.2001)). In this regard, pertinent art dictionaries, treatises, and encyclopedias may assist a court. *Texas Digital Sys., Inc. v. Telegenix, Inc.,* 308 F.3d 1193, 1202-03 (Fed.Cir.2002). The intrinsic record, however, is the best source of the meaning of claim language. *Vitronics Corp. v. Conceptronic, Inc.,* 90 F.3d 1576, 1582 (Fed.Cir.1996). Therefore, patent claims are properly construed only after an examination of the claims, the specification, and, if in evidence, the prosecution history of the patent. *Amgen, Inc. v. Hoechst Marion Roussel, Inc.,* 314 F.3d 1313, 1324 (Fed.Cir.2003) (citing *Vitronics,* 90

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F.3d at 1582).

*3 The intrinsic record is also of prime importance when claim language has no ordinary meaning in the pertinent art, *see* *Bell Atl. Network Servs., Inc. v. Covad Communications Group, Inc.,* 262 F.3d 1258, 1269-70 (2001) (determining that claim language could only be construed with reference to the written description) (citation omitted), and where claim language has multiple potentially applicable meanings, *Texas Digital, Inc.,* 308 F.3d at 1203.

If patent claim language has an ordinary and accustomed meaning in the art, there is a heavy presumption that the inventor intended that meaning to apply. *Bell Atl. Network Servs., Inc.,* 262 F.3d at 1268 (citing *Johnson Worldwide Assocs., Inc. v. Zebco Corp.,* 175 F.3d 985, 989 (Fed.Cir.1999)). Thus, unless the inventor has manifested an express intent to depart from that meaning, the ordinary meaning applies. *Teleflex, Inc. v. Ficosa N. Am. Corp.,* 299 F.3d 1313, 1325 (Fed.Cir.2002) (citation omitted).

To overcome that presumption, an accused infringer may demonstrate that "a different meaning is clearly set forth in the specification or ... the accustomed meaning would deprive the claim of clarity." *N. Telecom Ltd. v. Samsung Elecs. Co., Ltd.,* 215 F .3d 1281, 1287 (Fed.Cir.2000). However, the presumption may not be rebutted "simply by pointing to the preferred embodiment...." *Teleflex, Inc.,* 299 F.3d at 1327. It may be rebutted, though, where "the patentee ... deviate[d] from the ordinary and accustomed meaning ... by redefining the term or by characterizing the invention in the intrinsic record using words or expressions of manifest exclusion or restriction, representing a clear disavowal of claim scope." *Id.*

If claim language remains unclear after review of the intrinsic record, a court "may look to extrinsic evidence to help resolve the lack of clarity." *Interactive Gift Express, Inc. v. Compuserve Inc.,* 256 F.3d 1323, 1332 (Fed.Cir.2001). The use of extrinsic evidence in the claim construction process, however, is "proper only when the claim language remains genuinely ambiguous after consideration of the intrinsic evidence." *Id.* (citation omitted). A court may not use extrinsic evidence to contradict the import of the intrinsic record, and if the intrinsic record is unambiguous, extrinsic evidence is entitled to no weight. *Bell & Howell Document Mgmt. Prods. Co. v. Altek Sys.,* 132 F.3d 701, 706 (Fed.Cir.1997).

IV. CLAIM CONSTRUCTION

OGT alleges that Mergen literally infringes independent claims 1, 9, and 10 of the '270 patent. (D.I. 180 at 1.) Further, OGT alleges that Mergen contributorily infringes and/or actively induces others to infringe claims 9 and 10 as well. (*Id.;* D.I. 1 at 4.) Each claim will be discussed in turn, according to the claim terms in dispute.

A. CLAIM 1

Claim 1 of the '270 patent is as follows:

1. A method of making an array of oligonucleotides, which comprises:

*4 attaching a plurality of oligonucleotides to an impermeable surface of a support, the oligonucleotides having different predetermined sequences and being attached at different known locations on the surface of the support through a computer-controlled printing device.

'270 patent, col. 15, ll. 47-53.

1. "an array of oligonucleotides"

a. The Parties' Proposed Constructions

OGT argues that the preamble (i.e., the phrase "A method of making an array of oligonucleotides, which comprises:") is not limiting and therefore, does not require construction. (D.I. 174 at 9.) If found to be a limitation, OGT proposes that I construe the phrase "an array of oligonucleotides" to mean "two or more oligonucleotide sequences located at different regions on a single support." (*Id.;* D.I. 173 at 1.) Mergen proposes that I construe "an array of oligonucleotides" to mean "a single structured array of oligonucleotides having related sequences, such that the pattern of binding [FN6] of the sample polynucleotides to the oligonucleotides reveals the sequence of the sample polynucleotides."(D.I. 175 at 27; D.I. 209 at 5.)

FN6. Mergen uses the term "hybridization" in the Joint Claim Construction Chart, D.I. 173 at 1, instead of "binding," which it used in its Opening Claim Construction Brief, D.I. 175 at 27, and its Answering Brief, D.I. 209 at 5. The difference is negligible because I consider the terms essentially synonymous for the purpose of construing the phrase "an array of oligonucleotides" in claim 1

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of the '270 patent.

OGT argues that the preamble is not limiting and does not require construction. (D.I. 174 at 9.) If construed, OGT argues that this term is entitled to its ordinary and plain meaning. (D.I. 174 at 10.) The plain meaning of "an array" is a set of elements with two or more locations. (*Id.*) Mergen argues that the preamble needs to be construed because it gives meaning to the claim. (D.I. 209 at 5; D.I. 175 at 27-30.) Mergen further argues that there are two issues in dispute with regard to this claim term: (1) whether "an array" can be construed to mean more than one array, and (2) whether the "array of oligonucleotides" is a structured array of related sequences for sequencing analysis. (D.I. 175 at 27.) As to the latter, Mergen asserts that the answer is yes, the term is so limited. (*Id.* at 29.)It cites several parts of the specification that it believes support its proposed construction. (*Id.* at 28-29.)

b. The Court's Construction

A preamble is only limiting where "it recites essential structure or steps, or if it is necessary to give 'life, meaning, and vitality' to the claims."*Intirtool, Ltd. v. Texar Corp.*, 369 F.3d 1289, 1295 (Fed.Cir.2004) (internal quotations and citations omitted). If deletion of the preamble "does not affect the structure or steps of the invention," it should not be considered limiting unless there is "clear reliance on the preamble during prosecution to distinguish the claimed invention from the prior art. *Id.*(internal quotations and citations omitted).

While I do not think that the preamble's deletion affects "the structure or steps of the invention,"*id.*, to the extent that it is limiting, I agree with OGT's construction. This construction is consistent with the ordinary and plain meaning of "an array." I will not read limitations into the claim from the specification when the term is easily construed according to its ordinary meaning as understood by a person of ordinary skill in the art. *See Texas Digital Sys., Inc.*, 308 F.3d at 1205. Claim 1 states a method of making an array, not what uses that array may have, or what information may be gained by its use. Therefore, I do not accept Mergen's proposed construction. I construe "an array of oligonucleotides" to mean "two or more oligonucleotide sequences located at different regions on a single support."

2. "attaching a plurality of oligonucleotides"

a. The Parties' Proposed Construction

*5 OGT proposes that I construe "attaching a plurality of oligonucleotides" to mean "fastening (as by tying or gluing) or affixing two or more oligonucleotides."(D.I. 174 at 12; D.I. 173 at 1.) Mergen proposes that I construe "attaching a plurality of oligonucleotides to mean "monomer by monomer synthesis of oligonucleotides on an impermeable surface of a support."(D.I. 175 at 13; D.I. 209 at 9; D.I. 173 at 1.)

The focus of the parties' dispute in this claim term is the word "attaching." [FN7]OGT argues that "attaching" should be construed according to its ordinary and plain meaning. (D.I. 175 at 12.) Mergen argues that I should read into the term "attaching," the *method* by which the oligonucleotides are attached. (D.I. 175 at 13.) In support of its proposed construction, Mergen relies on a theory of prosecution disclaimer. (D.I. 175 at 16-18.) [FN8]

FN7. It does not appear that the parties contest that the phrase "a plurality of oligonucleotides" means "two or more oligonucleotides ." Therefore, I need not construe it further.

FN8. Mergen, however, has not carried its burden of demonstrating a clear and unambiguous disclaimer with respect to this claim term. *See Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1324 (Fed.Cir.2003).

b. The Court's Construction

"Attaching" is a common, everyday word. As discussed above, I will not read in limitations from the specification when the term is easily construed according to its ordinary meaning as understood by a person of ordinary skill in the art. *See Texas Digital Sys., Inc .*, 308 F.3d at 1205. To construe "attaching a plurality of oligonucleotides," I do not need to find further limitations regarding the *method* of attachment. "Attaching," when read in light of the specification means "affixing." Therefore, I construe "attaching a plurality of oligonucleotides" to mean "affixing two or more oligonucleotides."

3. "to an impermeable surface of a support"

a. The Parties' Proposed Constructions

OGT proposes that I construe "to an impermeable surface of a support" to mean to "a side of a single, mostly flat

solid having a non-porous surface that does not permit diffusion through its substance."(D.I. 175 at 15; D.I. 173 at 1.) Mergen proposes that I construe "to an impermeable surface of a support" to mean either: to "a solid having a non-porous surface that does not permit diffusion through its substance," FN9 (D.I. 173 at 1), or to "the surface of the support is a solid, non-porous surface that is impermeable to liquid applied to the surface such that it prohibits diffusion."(D.I. 175 at 10; D.I. 209 at 16.) FN10

FN9. This is the same construction that OGT proposed in litigation against Motorola regarding essentially the same claim term, in the context of claim 9 of the '270 patent. (D.I. 176, Ex. B at 11.)

FN10. At the *Markman* Hearing, in response to questioning regarding which construction Mergen proposes at the present time, counsel for Mergen responded: "Either construction is fine." (D.I. 269 at 98:1-98:2) (transcript for *Markman* Hearing, August 27, 2004.)

b. The Court's Construction

The focus of the parties dispute is the term "a support" because both parties propose identical constructions regarding the "impermeable surface." (D.I. 173 at 1.) I find little or no basis for OGT's proposed construction that the support is *"a side of a single, mostly flat* solid."(*Id.* (emphasis added).) There is no indication in the specification that the support is "mostly flat ." While a "surface" may be considered "a side" of an object, the clear and plain meaning of "surface" is "the exterior or outside of an object or body."WEBSTER'S THIRD NEW INTERNATIONAL DICTIONARY OF THE ENGLISH LANGUAGE 2300 (1986). Even OGT uses the term "surface" in the latter part of its proposed construction, indicating that it does not believe "surface" requires further construction. (D.I. 174 at 15-16; D.I. 173 at 1.) Therefore, I construe "to an impermeable surface of a support" to mean "to a solid having a non-porous surface that does not permit diffusion through its substance."

4. "the oligonucleotides having different predetermined sequences and being attached at different known locations on the surface of the support"

a. The Parties' Proposed Constructions

***6** OGT's proposes that I construe "the oligonucleotides having different predetermined sequences and being attached at different known locations on the surface of the support" to mean "the oligonucleotides having different predetermined sequences and being affixed or fastened to the support surface at different known locations."(D.I. 174 at 16; D.I. 173 at 2.) Mergen proposes that I construe "the oligonucleotides having different predetermined sequences and being attached at different known locations on the surface of the support" to mean "the sequences of the different oligonucleotides are known" and that "the oligonucleotides *themselves* are attached to the impermeable surface such that the different oligonucleotides occupy separate regions of the array."(D.I. 173 at 2; see D.I. 209 at 17-20 (emphasis added).)

b. The Court's Construction

In the Joint Claim Construction Chart, the parties agreed that the only disputed claim term in the above quoted claim language is "being attached." FN11(D.I. 173 at 2.) In regards to this claim term, the word "attached" is the focus of attention. (*Id.*) In general, both parties make the same arguments made in section IV.A.2 .a., *supra* at 10.Mergen also argues that the oligonucleotides *themselves* are attached to the impermeable surface.(*Id.* (emphasis added).) Mergen, however, does not explain in its Opening Claim Construction Brief or Answering Brief why the term "attached" in this part of claim 1 should include the word "themselves," when Mergen did not introduce that construction when "attached" was to be construed. I do not include the word "themselves" because it is clear from the patent that the oligonucleotides themselves are not attached to the impermeable surface, but rather are attached via a linker which is attached to the surface. (D.I. 174 at 17.) For example, the specification states:

FN11. OGT stated: "The only disputed term included in this phrase is 'attached'...." (D.I. 173 at 2.) Mergen stated that "the oligonucleotides having different predetermined sequences" was agreed to by the parties to mean "the sequences of the different oligonucleotides are known" and that "at different known locations on the surface of the support was agreed to mean "that the oligonucleotides are bound to the surface of the support, such that the different oligonucleotides occur separate regions of the array."(D.I. 173 at 2.)

Commercially available microscope slides (BDH Super

Premium 76x26x1 mm) were used as supports. These were derivatised with a long aliphatic linker that can withstand conditions used for the deprotection of the aromatic heterocyclic bases, i.e. 30% NH3 at 55 for 10 hours. The *linker,* bearing a hydroxyl group which *serves as a starting point for the subsequent oligonucleotide,* is synthesised in two steps.

'270 patent, col. 8, ll. 59-65 (emphasis added). Therefore, I construe "being attached" to mean simply "being affixed."

5. "through a computer-controlled printing device"

a. The Parties' Proposed Constructions

OGT provides no proposed construction for "through a computer-controlled printing device" and only repeats the words "through a computer-controlled printing device." (D.I. 174 at 17; D.I. 173 at 2.) Mergen proposes that I construe "through a computer-controlled printing device" to mean "the monomer by monomer synthesis of oligonucleotides *to* known locations on the impermeable surface of the support is done with a computer-controlled printing device."FN12(D.I. 175 at 18 (emphasis added).)

FN12. In the parties Joint Claim Construction Chart, Mergen proposed that I construe "through a computer-controlled printing device" to mean "the monomer by monomer synthesis of oligonucleotides *at* known locations on the impermeable surface of the support is done with a computer-controlled printing device."(D.I. 173 at 2 (emphasis added).)

b. The Court's Construction

*7 Reading the claim in light of the specification requires me to construe "through a computer-controlled printing device" to mean "through a computer-controlled printing device using monomer by monomer synthesis of oligonucleotides."I reach this conclusion after careful consideration of the claim term and the specification. Although OGT argues that claim 1 covers both the *in situ* and deposition methods of oligonucleotide synthesis (D.I. 174 at 18), the specification does not support the conclusion that a computer-controlled printing device can perform the deposition method.

Specifically, OGT points to three places in the specification for support. First, column 6, lines 51-55 of the '270 patent state: "Laying down very large number of lines or dots could take a long time, if the printing mechanism were slow. However, a low cost inkjet printer can print at speeds of about 10,000 spots per second."OGT uses this as support for the decreased time spent manufacturing an array by using an inkjet printer. (D.I. 174 at 18.)

This example supports the proposition that inkjet printers reduce the time required to manufacture an array. This quotation, however, comes from a section entitled, "5.2 Laying Down the Matrix." '270 patent, col. 6, ll. 29-56. The first five lines of this section clearly disclose the *in situ* method of building oligonucleotides on the array. "The method described here envisages that the matrix will be produced by *synthesising oligonucleotides in the cells of an array* by laying down the precursors for the four bases in a predetermined patten, an example of which is described above."(*Id.* at ll. 31-35 (emphasis added).) There is no disclosure in this section that supports OGT's proposition that inkjet printers can also be used for depositing *pre-formed* oligonucleotides. Therefore, according to the claim language and the disclosure in the specification, the time advantage referred to above is in the context of the *in situ* method of synthesizing oligonucleotides.

The second place OGT cites to support its argument that the specification discloses the deposition method of oligonucleotide synthesis is Section 5.3 entitled: "Oligonucleotide Synthesis." "Although we know of no description of the direct use of oligonucleotides as hybridisation probes while still attached to the matrix on which they were synthesised, there are reports of the use of oligonucleotides as hybridisation probes on solid supports to which they were attached *after* synthesis."(D.I. 1, Ex.1, col. 6 line 63 through col. 7 line 1 (emphasis added).) This disclosure does refer to the deposition method, but does not provide support for OGT's argument that claim 1 includes this method. If anything, this disclosure seems to support Mergen's argument that: "This patent is a teaching of the new technology.... The only time they mention a deposit method, they talk about the known prior art, which they're just changing their patent from."(D.I. 269 at 72:18-73:3) Therefore, I do not believe that this disclosure gives added support to OGT's argument.

***8** The third place in the specification that OGT cites for its construction is Example 5 which states: "A microcomputer was used to control the plotter and the syringe pump which delivered the chemicals."'270 patent, col. 11, ll. 52-53. This example, however, continues: "Filling the pen

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*successively* with G, T and A phosphoramidite solutions an array of twelve spots was laid down in three groups of four, with three different oligonucleotide sequences ." '270 patent, col. 11, ll. 57-60 (emphasis added).) Reading Example 5 in full, makes it clear that it discloses the use of a microcomputer to control the *in situ* method of oligonucleotide synthesis because the nucleotides are filled "successively." This is different than depositing a preformed oligonucleotide as would be required in the deposition method.FN13

FN13. OGT makes another argument in its Answering Brief which seems to suggest that Example 5 does not even apply to claim 1. "Meanwhile, claim 7, contains a limitation to a computer-controlled printing device. Since it depends from claim 3, claim 7 is limited to *in situ* synthesis by its own terms. And because it is limited to *in situ* synthesis, claim 7 recites attaching 'nucleotide *precursors.* 'Claim 1 does *not* apply 'nucleotide *precursors* . " ' (D.I. 222 at 15-16 (emphasis added).)

This argument by OGT seems to contradict its reliance on Example 5 for disclosing support for the deposition method of oligonucleotide synthesis. Example 5 begins with the phrase, "To test an automated system for laying down the *precursors....* " (D .I. 1, Ex. 1, col. 11, ll. 42-43 (emphasis added).) If Example 5 does not pertain to claim 1, as OGT seems to suggest, then OGT has eliminated that example as support for its argument that claim 1 is not limited to *in situ* oligonucleotide synthesis.

Based on the foregoing, I conclude that the language of the claim, when read in light of the disclosures in the specification, supports the conclusion that "through a computer-controlled printing device" means "through a computer-controlled printing device using monomer by monomer synthesis of oligonucleotides."

Even if this construction were not sufficiently clear from the patent itself, the prosecution history also supports this interpretation. Original claims 36 and 37 of what became the '270 patent were as follows:

36. A method of making an array of oligonucleotides, which comprises:

attaching a plurality of oligonucleotides to an impermeable surface of a support, the oligonucleotides having different predetermined sequences and being attached at different known locations on the surface of the support.

37. The method as claimed in claim 36 or 111, wherein the oligonucleotides are synthesized before attachment to the surface of the support.

(D.I. 201, Ex. D at 4.) (Declaration of Philip Rovner.) After amendment, claim 36 became claim 1, as discussed above. The prosecution history provides evidence for the motive behind the amendment to add the language "through a computer-controlled printing device" at the end of the claim. (D.I. 201, Ex. D at 4.) The examiner rejected claim 37 under 35 U.S.C. § 112, first paragraph, as containing "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention."(D .I. 201, Ex. E at 2.) The basis for the rejection was that: "The 'synthesis' *before* attachment of claim 37 has not been found."(*Id.* (emphasis added).) In other words, a claim including the deposition method was not supported by the specification. The applicant cancelled claim 37 in response to this rejection. (D.I. 201, Ex. F at 1.) And finally, when claim 36 was eventually allowed, the examiner stated: "Stavrianopoulos et al. (U.S. Patent No. 4,994,373) is the closest prior art of record *but neither teaches nor suggests monomer by monomer synthesis of oligonucleotides* on a surface nor the hybridization assay practice of utilizing an array of different oligonucleotide probes on a single surface."FN14(D.I. 201, Ex. H at 4 (emphasis added).)

FN14. OGT has argued that this statement by the examiner specifically refers to only claims 3 through 8 and not claim 1. When asked to provide a basis for this argument, other than "generalized reasoning," counsel for OGT simply stated, "So my answer is, no, I can't do that, Your Honor."(D.I. 269 at 45:22-23.) Therefore, I do not find any basis for limiting the examiner's comments to only claims 3 through 8.

*9 This prosecution history suggests: (1) that the examiner did not find support in the specification for the deposition method, evidenced by his rejection of claim 37's "synthesis before attachment;" (2) the amendment to original claim 36, adding "through a computer-controlled printing device," limited claim 36 to monomer by monomer synthesis because otherwise, the examiner would have

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rejected it for the same reason he rejected claim 37; and (3) at least one reason that the examiner allowed the claim is because it taught monomer by monomer synthesis, which distinguished it over the closest prior art. Therefore, the prosecution history supports the conclusion that "through a computer-controlled printing device" means "through a computer-controlled printing device using monomer by monomer synthesis of oligonucleotides."

B. CLAIM 9

Claim 9 of the '270 patent is as follows:

9. A method of analysing a polynucleotide, which method comprises:

applying a labelled polynucleotide to be analysed or fragments thereof to an array of oligonucleotides under hybridisation conditions, wherein the array comprises a support having an impermeable surface to which a plurality of oligonucleotides having different predetermined sequences are attached to different known regions on the surface, and

analysing the polynucleotide by observing the regions where the polynucleotide or fragment thereof hybridizes and the regions where the polynucleotide or fragment thereof does not hybridize.

'270 patent, col. 16, ll. 44-56.

1. "analysing a polynucleotide"

a. The Parties' Proposed Constructions

OGT argues that the preamble is not limiting and therefore, does not require construction. (D.I. 174 at 19.) If found to be a limitation, OGT proposes that I construe the phrase "analysing a polynucleotide" to mean "determining information about one or more polynucleotides, which includes detecting the presence or quantity of one or more polynucleotides."(D.I. 173 at 3.) Mergen proposes that I construe the phrase "analysing a polynucleotide" to mean "the process of which determining information about the sequence of a polynucleotide whose identity is incompletely known, as defined by the subsequent steps of the claim."(D.I. 175 at 20; D.I. 173 at 3.)

b. The Court's Construction

As earlier noted, *supra* at 9, a preamble is only limiting where "it recites essential structure or steps, or if it is necessary to give 'life, meaning, and vitality' to the claims."*Intirtool, Ltd.,* 369 F.3d at 1295 (internal quotations and citations omitted). If deletion of the preamble "does not affect the structure or steps of the invention," it should not be considered limiting unless there is "clear reliance on the preamble during prosecution to distinguish the claimed invention from the prior art. *Id.*(internal quotations and citations omitted).

While I do not think that the preamble's deletion affects "the structure or steps of the invention,"*id.,* to the extent that the preamble may be viewed as limiting, the parties do not dispute the construction. In its Answering Brief, OGT states that: "If Mergen simply means 'the process of which determining information about the sequence of one or more polynucleotides whose identity is incompletely known'... OGT has no issue with that construction...." (D.I. 222 at 21.) This is essentially the same construction Mergen offered. Therefore, even if the preamble were limiting, the term is evidently not in dispute and I will not construe it.

2. "to an array of oligonucleotides"

a. The Parties' Proposed Constructions

***10** OGT proposes that I construe "to an array of oligonucleotides" to mean "to a set of two or more oligonucleotide sequences located at different regions on a single support."(D.I. 174 at 20; D.I. 173 at 3.) Mergen proposes that I construe "to an array of oligonucleotides" to mean to "a single structured array of oligonucleotides having related sequences, such that the pattern of binding [FN15] of the sample polynucleotides to the oligonucleotides reveals the sequence of the sample polynucleotides."(D.I. 175 at 27; D.I. 209 at 5.)

FN15.*See* n. 5, *supra.*

b. The Court's Construction

The phrase "to an array of oligonucleotides" is substantively identical to the claim term construed in Claim 1, see *supra,* section IV.A.1.b. Therefore, I construe "to an array of oligonucleotides" to mean "to two or more oligonucleotide sequences located at different regions on a single support."

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3. "under hybridisation conditions"

a. The Parties' Proposed Constructions

OGT proposes that I construe "under hybridisation conditions to mean "under conditions suitable for hybridization." (D.I. 174 at 21; D.I. 173 at 4.) Mergen proposes that I construe "under hybridisation conditions" to mean "conditions that permit discrimination between hybridization of oligonucleotide sequences that are exactly matched and mismatched to the polynucleotide sequence."(D.I. 175 at 23; D.I. 173 at 4.)

b. The Court's Construction

OGT argues that this claim term should be construed according to its plain and ordinary meaning. (D.I. 174 at 21.) Mergen encourages me to read in limitations from the specification. (D.I. 175 at 23-24 .) I will not read in limitations from the specification when the term is easily construed according to its ordinary meaning as understood by a person of ordinary skill in the art. *See* Texas Digital Sys., Inc., 308 F.3d at 1205. I conclude that one of ordinary skill in the art would understand that the phrase "under hybridisation conditions" means "under conditions suitable for hybridization." Therefore, I construe the phrase "under hybridisation conditions" to mean "under conditions suitable for hybridization."

4. "wherein the array comprises a support having an impermeable surface to which a plurality of oligonucleotides having different predetermined sequences are attached to different known regions on the surface"

a. The Parties' Proposed Constructions

The parties agree that the only claim terms from the quoted language that are in dispute are "a support having an impermeable surface" and "are attached." (D.I. 173 at 4-5.) OGT proposes that I construe this passage to mean "wherein the array comprises a side of a single, mostly flat solid having a non-porous surface that does not permit diffusion through its substance and to which two or more oligonucleotides having different predetermined sequences are fastened or affixed to different known regions on the surface."(D.I. 174 at 23; D.I. 173 at 4.) Mergen refers me back to its proposed constructions of the terms as they previously appeared in claim 1.[FN16] (D.I. 209 at 28.)

FN16. Specifically, Mergen proposes that I construe: (1) "a support having an impermeable surface" to mean "a solid having a non-porous surface that does not permit diffusion through its substance;" (2) "a plurality of oligonucleotides having different predetermined sequences" to mean "the sequences of the different oligonucleotides are known;" (3) "are attached" to mean "that the oligonucleotides themselves are attached to the impermeable surface;" and (4) "to different known regions on the surface" to mean "that the oligonucleotides are bound to the surface of the support, such that the different oligonucleotides occupy separate regions of the array."(D.I. 173 at 4-5.)

b. The Court's Construction

*11 Essentially the same terms have been construed in Claim 1, with insignificant differences.[FN17] I have construed "attaching a plurality of oligonucleotides" to mean "affixing two or more oligonucleotides." *See supra,* section IV.A.2.b. I have construed "to an impermeable surface of a support" to mean "to a solid having a non-porous surface that does not permit diffusion through its substance."*See supra,* section IV.A.3.b. And I have construed "being attached" to mean "being affixed." *See supra,* section IV.A.4.b.

FN17. Two insignificant differences are that claim 1 reads: "*being* attached at different known *locations* on the surface," '270 patent, col. 15 ll. 51-52 (emphasis added), whereas claim 9 reads: "*are* attached to different known *regions* on the surface." '270 patent, col. 16, ll. 50-52 (emphasis added). These minor differences do not change the claim terms previously construed in any significant way. In addition, the latter portions of each claim, "at different known locations" and "to different known regions," were not directly disputed. *See supra,* sections IV.A.2. through IV.A.4.

5. "analysing the polynucleotide"

a. The Parties' Proposed Constructions

OGT proposes that I construe "analysing the polynucleotide" to mean "determining information about

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one or more polynucleotides, which includes detecting the presence or quantity of one or more polynucleotides."(D.I. 174 at 25; D.I. 173 at 5.) Mergen proposes that I construe "analysing the polynucleotide" to mean "the process of which determining information about the sequence of a polynucleotide whose identity is incompletely known."(D.I. 175 at 20; D.I. 173 at 5.)

b. The Court's Construction

This is the same claim term discussed above in the preamble of claim 9. *See supra,* section IV.B.1. In its Answering Brief, OGT states that: "If Mergen simply means 'the process of which determining information about the sequence of one or more polynucleotides whose identity is incompletely known'... OGT has no issue with that construction...." (D.I. 222 at 21.) As discussed in section IV.B.1., *supra,* this is essentially the same construction Mergen offered. Therefore, because this claim term evidently is not in dispute, I need not construe it.

6. "by observing the regions where the polynucleotide or fragment thereof hybridizes and the regions where the polynucleotide or fragment thereof does not hybridize"

a. The Parties' Proposed Constructions

OGT proposes that I construe the above quoted language to mean "by observing the regions where the polynucleotide or fragment thereof hybridizes and where it does not."(D.I. 174 at 25; D.I. 173 at 5.) Mergen proposes that I construe it to mean "information about more than one polynucleotide sequence is gained by comparing the locations of hybridization and no hybridization."(D.I. 175 at 24-25; D.I. 173 at 5.)

b. The Court's Construction

OGT argues that the plain and ordinary meaning should be used to interpret this claim, D.I. 174 at 25, and I agree. Observing means looking. This claim term essentially instructs one to look at the regions where hybridization has occurred and the regions where hybridization has not occurred. It is that simple. I do not find that this claim term needs to be limited to what, if any, information is gained by observing. Therefore, I construe "by observing the regions where the polynucleotide or fragment thereof hybridizes and the regions where the polynucleotide or fragment thereof does not hybridize" to mean exacting what it says "by observing the regions where the polynucleotide or fragment thereof hybridizes and the regions where the polynucleotide or fragment thereof does not hybridize."

C. CLAIM 10

***12** Claim 10 of the '270 patent is as follows:

10. A method of comparing polynucleotide sequences, which method comprises:

applying the polynucleotides to an array of oligonucleotides under hybridizing conditions, wherein the oligonucleotides have different predetermined sequences and are attached at different known locations on an impermeable surface of a support, and

observing the differences between the patterns of hybridisation.

'270 patent, col. 16, ll. 57-65.

1. "comparing polynucleotide sequences"

a. The Parties' Proposed Constructions

OGT proposes that I construe "comparing polynucleotide sequences" to mean "determining relative information about two or more polynucleotides."(D.I. 174 at 27; D.I. 173 at 5.) [FN18] Mergen proposes that I construe "comparing polynucleotide sequences" to mean "the process of determining relative information about two or more polynucleotide sequences, as defined by the subsequent steps of the claim."(D.I. 175 at 26; D.I. 173 at 5.)

FN18. OGT argues that the preamble should be construed in this claim because the claim language refers back to the phrase "the polynucleotide sequences." (D.I. 174 at 27.) OGT, however, does not suggest that the preamble has to be construed, only that it would be helpful for me to construe it "for legal precision ... although the term could also be construed when it appears in the claim element itself."(*Id.*) When "the body of the claim fully and intrinsically sets forth the complete invention, including all of its limitations ... the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation."*Pitney Bowes, Inc. v.*

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Hewlett-Packard Co., 182 F.3d 1298, 1305 (Fed.Cir.1999) (internal citations omitted). My process for construing the preamble of this claim is consistent with that used to construe the preamble of claims 1 and 9. *See supra* pp. 9 and 19-20.

b. The Court's Construction

As earlier noted, *supra* at 9, a preamble is only limiting where "it recites essential structure or steps, or if it is necessary to give 'life, meaning, and vitality' to the claims."*Intirtool, Ltd.,* 369 F.3d at 1295 (internal quotations and citations omitted). If deletion of the preamble "does not affect the structure or steps of the invention," it should not be considered limiting unless there is "clear reliance on the preamble during prosecution to distinguish the claimed invention from the prior art. *Id.*(internal quotations and citations omitted).

While I do not think that the preamble's deletion affects "the structure or steps of the invention,"*id.,* to the extent that the preamble may be viewed as limiting, I construe "comparing polynucleotide sequences" to mean "the process of determining relative information about two or more polynucleotide sequences."

2. "applying the polynucleotides to an array of oligonucleotides under hybridizing conditions, wherein the oligonucleotides have different predetermined sequences and are attached at different known locations on an impermeable surface of a support"

a. The Parties' Proposed Constructions

OGT and Mergen each propose that I construe these claim terms in the same manner as they have each proposed with respect to earlier claim language. (D.I. 174 at 28-29; D.I. 209 at 31; D.I. 173 at 6-7.)

b. The Court's Construction

I agree with the parties and construe "applying the polynucleotides to an array of oligonucleotides under hybridizing conditions, wherein the oligonucleotides have different predetermined sequences and are attached at different known locations on an impermeable surface of a support" to be consistent with the earlier constructions. More specifically, I have construed "an array of oligonucleotides" to mean "two or more oligonucleotide sequences located at different regions on a single support."*See supra,* section IV.A.1.b. I have construed "under hybridising conditions" to mean "under conditions suitable for hybridization." *See supra,* section IV.B.3.b. I have construed "attached" (the only term actually in dispute) to mean "affixed." *See supra,* section IV.A.4.b. And I have construed "to an impermeable surface of a support" to mean "to a solid having a non-porous surface that does not permit diffusion through its substance."*See supra,* section IV.A.3.b.

3. "observing the differences between the patterns of hybridisation"

a. The Parties' Proposed Constructions

***13** OGT proposes that I construe "observing the differences between the patterns of hybridisation" to mean "observing the differences between the patterns of hybridization."(D.I. 174 at 29; D.I. 173 at 7.) Mergen proposes that I construe "observing the differences between the patterns of hybridisation" to mean "information about more than one polynucleotide sequence is gained by analysing patterns of hybridization."(D.I. 173 at 7.)

b. The Court's Construction

OGT argues that this claim term should be construed according to its ordinary and plain meaning. (D.I. 174 at 29.) I agree. As earlier noted, the word "observing" has a plain and ordinary meaning which is synonymous with "looking." *See supra,* section IV.B.6.b. Mergen argues that I should read limitations into this claim term from the specification. (D.I. 175 at 32-33.) What, if any, information is gained by observing the differences between the patterns of hybridisation is not a limitation of this claim term. Therefore, I construe "observing the differences between the patterns of hybridisation" to mean exactly what it says, "observing the differences between the patterns of hybridization."

V. CONCLUSION

| CLAIM TERM/PHRASE | THE COURT'S CONSTRUCTION |
| --- | --- |

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| | |
|---|---|
| Claim 1: | |
| "an array of oligonucleotides" | The Court construes the claim term "an array of oligonucleotides" to mean "two or more oligonucleotide sequences located at different regions on a single support." |
| "attaching a plurality of oligonucleotides" | The Court construes the claim term "attaching a plurality of oligonucleotides" to mean "affixing two or more oligonucleotides." |
| "to an impermeable surface of a support" | The Court construes the claim term "to an impermeable surface of a support" to mean "to a solid having a non-porous surface that does not permit diffusion through its substance." |
| "the oligonucleotides having different predetermined sequences and being attached at different known locations on the surface of the support" | The Court construes the claim term "being attached" to mean "being affixed." |
| "through a computer-controlled printing device" | The Court construes the claim term "through a computer-controlled printing device" to mean "through a computer-controlled printing device using monomer by monomer synthesis of oligonucleotides." |

| CLAIM TERM/PHRASE | THE COURT'S CONSTRUCTION |
|---|---|
| Claim 9: | |
| "to an array of oligonucleotides" | The Court construes the claim term "to an array of oligonucleotides" to mean "to two or more oligonucleotide sequences located at different regions on a single support." |
| "under hybridisation conditions" | The Court construes the claim term "under hybridisation conditions" to mean "under conditions suitable for hybridization." |
| "wherein the array comprises a support having an impermeable surface to | The Court construes the claim term "a support having an impermeable surface" |

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| | |
|---|---|
| which a plurality of oligonucleotides having different predetermined sequences are attached to different known regions on the surface" | to mean "to a solid having a non-porous surface that does not permit diffusion through its substance."<br><br>The Court construes the claim term "are attached" to mean "are affixed." |
| "by observing the regions where the polynucleotide or fragment thereof hybridizes and the regions where the polynucleotide or fragment thereof does not hybridize" | The Court construes the claim term "by observing the regions where the polynucleotide or fragment thereof hybridizes and the regions where the polynucleotide or fragment thereof does not hybridize" to mean "by observing the regions where the polynucleotide or fragment thereof hybridizes and the regions where the polynucleotide or fragment thereof does not hybridize." |

| CLAIM TERM/PHRASE | THE COURT'S CONSTRUCTION |
|---|---|
| Claim 10:<br>"comparing polynucleotide sequences" | The Court construes the claim term "comparing polynucleotide sequences" to mean "the process of determining relative information about two or more polynucleotide sequences." |
| "applying the polynucleotides to an array of oligonucleotides under hybridizing conditions, wherein the oligonucleotides have different predetermined sequences and are attached at different known locations on an impermeable surface of a support" | The Court construes the claim term "an array of oligonucleotides" to mean "two or more oligonucleotide sequences located at different regions on a single support."<br><br>The Court construes the claim term "under hybridizing conditions" to mean "under conditions suitable for hybridization."<br>The Court construes the claim term "are attached" to mean "are affixed."<br>The Court construes the claim term "on an impermeable surface of a support" to mean "on a solid having a non-porous |

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| | |
|---|---|
| | surface that does not permit diffusion through its substance." |
| "observing the differences between the patterns of hybridisation" | The Court construes the claim term "observing the differences between the patterns of hybridisation" to mean "observing the differences between the patterns of hybridization." |

***14** An appropriate order will issue.

*ORDER*

For the reasons set forth in the Opinion issued today, IT IS HEREBY ORDERED that the disputed claim terms in U.S. Patent No. 6,054,270 is construed as follows:

| CLAIM TERM/PHRASE | THE COURT'S CONSTRUCTION |
|---|---|
| Claim 1: | |
| "an array of oligonucleotides" | The Court construes the claim term "an array of oligonucleotides" to mean "two or more oligonucleotide sequences located at different regions on a single support." |
| "attaching a plurality of oligonucleotides" | The Court construes the claim term "attaching a plurality of oligonucleotides" to mean "affixing two or more oligonucleotides." |
| "to an impermeable surface of a support" | The Court construes the claim term "to an impermeable surface of a support" to mean "to a solid having a non-porous surface that does not permit diffusion through its substance." |
| "the oligonucleotides having different predetermined sequences and being attached at different known locations on the surface of the support" | The Court construes the claim term "being attached" to mean "being affixed." |
| "through a computer-controlled printing device" | The Court construes the claim term "through a computer-controlled printing device" to mean "through a computer-controlled printing device using monomer by monomer synthesis of oligonucleotides." |

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| CLAIM TERM/PHRASE | THE COURT'S CONSTRUCTION |
| --- | --- |
| Claim 9: | |
| "to an array of oligonucleotides" | The Court construes the claim term "to an array of oligonucleotides" to mean "to two or more oligonucleotide sequences located at different regions on a single support." |
| "under hybridisation conditions" | The Court construes the claim term "under hybridisation conditions" to mean "under conditions suitable for hybridization." |
| "wherein the array comprises a support having an impermeable surface to which a plurality of oligonucleotides having different predetermined sequences are attached to different known regions on the surface" | The Court construes the claim term "a support having an impermeable surface" to mean "to a solid having a non-porous surface that does not permit diffusion through its substance." |
| | The Court construes the claim term "are attached" to mean "are affixed." |
| "by observing the regions where the polynucleotide or fragment thereof hybridizes and the regions where the polynucleotide or fragment thereof does not hybridize" | The Court construes the claim term "by observing the regions where the polynucleotide or fragment thereof hybridizes and the regions where the polynucleotide or fragment thereof does not hybridize" to mean "by observing the regions where the polynucleotide or fragment thereof hybridizes and the regions where the polynucleotide or fragment thereof does not hybridize." |

| CLAIM TERM/PHRASE | THE COURT'S CONSTRUCTION |
| --- | --- |
| Claim 10: | |
| "comparing polynucleotide sequences" | The Court construes the claim term "comparing polynucleotide sequences" to mean "the process of determining relative information about two or more polynucleotide sequences." |
| "applying the polynucleotides to an array | The Court construes the claim term "an |

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| | |
|---|---|
| of oligonucleotides under hybridizing conditions, wherein the oligonucleotides have different predetermined sequences and are attached at different known locations on an impermeable surface of a support" | array of oligonucleotides" to mean "two or more oligonucleotide sequences located at different regions on a single support." <br> The Court construes the claim term "under hybridizing conditions" to mean "under conditions suitable for hybridization." <br> The Court construes the claim term "are attached" to mean "are affixed." <br> The Court construes the claim term "on an impermeable surface of a support" to mean "on a solid having a non-porous surface that does not permit diffusion through its substance." |
| "observing the differences between the patterns of hybridisation" | The Court construes the claim term "observing the differences between the patterns of hybridisation" to mean "observing the differences between the patterns of hybridization." |

D.Del.,2004.
Oxford Gene Technology Ltd. v. Mergen Ltd.
Not Reported in F.Supp.2d, 2004 WL 2211971 (D.Del.)

END OF DOCUMENT

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## X. RELATED PROCEEDINGS APPENDIX

(4) Opinion and Order on Motions for Summary Judgment, Oxford Gene Technology Ltd. v. Mergen Ltd., et al., Civil Action No. 02-1695-KAJ before the United States District Court for the District of Delaware, 345 F.Supp.2d. 444, November 19, 2004.

**H**Oxford Gene Technology Ltd. v. Mergen Ltd.
D.Del.,2004.

United States District Court,D. Delaware.
OXFORD GENE TECHNOLOGY LIMITED, Plaintiff,
v.
MERGEN LTD., et al., Defendants.
**No. CIV.A.C2-1695-KAJ.**

Nov. 19, 2004.

**Background:** Owner of patent for method of analyzing polynucleotide sequences sued competitor for infringement. Parties cross-moved for summary judgment on issues of infringement and validity.

**Holdings:** The District Court, Jordan, J., held that:
(1) patent was not invalid as anticipated;
(2) fact issue existed as to whether patent was invalid as obvious;
(3) claim calling for monomer by monomer synthesis of oligonucleotides on substrate was not infringed;
(4) claimed polynucleotide analysis method was infringed;
(5) competitor was liable for induced infringement; and
(6) competitor was contributorily liable for its customers' direct infringement.

Motions granted in part and denied in part.

See also 2004 WL 2211971 and 2004 WL 2632933.

West Headnotes

**[1] Patents 291 ⚷112.5**

291 Patents
291IV Applications and Proceedings Thereon
291k112 Conclusiveness and Effect of Decisions of Patent Office
291k112.5 k. Sufficiency of Evidence to Offset Effect of Decision in General. Most Cited Cases
Party asserting patent's invalidity bears burden to establish invalidity by clear and convincing evidence.

**[2] Patents 291 ⚷112.1**

291 Patents
291IV Applications and Proceedings Thereon
291k112 Conclusiveness and Effect of Decisions of Patent Office
291k112.1 k. In General. Most Cited Cases
Although burden of proving patent invalidity never shifts from party asserting invalidity, burden of going forward with evidence rebutting invalidity may shift to patentee once party asserting invalidity has demonstrated legally sufficient prima facie case of invalidity.

**[3] Patents 291 ⚷226.6**

291 Patents
291XII Infringement
291XII(A) What Constitutes Infringement
291k226.5 Substantial Identity of Subject Matter
291k226.6 k. Comparison with Claims of Patent. Most Cited Cases
Patent infringement analysis involves two steps: claim construction, which is purely matter of law, and then application of construed claim to accused process or product, which is fact-specific inquiry.

**[4] Patents 291 ⚷323.2(2)**

291 Patents
291XII Infringement
291XII(C) Suits in Equity
291k323 Final Judgment or Decree
291k323.2 Summary Judgment
291k323.2(2) k. Presence or Absence of Fact Issues. Most Cited Cases
Summary judgment is appropriate in patent infringement suit when it is apparent that only one conclusion regarding infringement could be reached by reasonable jury.

**[5] Patents 291 ⚷72(1)**

291 Patents
291II Patentability
291II(D) Anticipation
291k72 Identity of Invention
291k72(1) k. In General. Most Cited Cases
Patent anticipation requires that each and every element of claimed invention be disclosed in single prior art reference; if any claimed element is missing from prior art reference,

(4)

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it cannot anticipate claimed invention. 35 U.S.C.A. § 102.

**[6] Patents 291 66(1.24)**

291 Patents
291II Patentability
291II(D) Anticipation
291k63 Prior Patents
291k66 Operation and Effect
291k66(1.24) k. Process, Method, and Apparatus Claims in General. Most Cited Cases
Patent for method of analyzing polynucleotide sequences, calling for attachment of oligonucleotides to impermeable surface, was not anticipated by prior art which did not disclose impermeable support surface. 35 U.S.C.A. § 102.

**[7] Patents 291 16.13**

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16.13 k. Fact Questions. Most Cited Cases
Ultimate determination of patent obviousness is question of law based on underlying factual inquiries. 35 U.S.C.A. § 103(a).

**[8] Patents 291 16(2)**

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16 Invention and Obviousness in General
291k16(2) k. Prior Art in General. Most Cited Cases

**Patents 291 16(3)**

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16 Invention and Obviousness in General
291k16(3) k. View of Person Skilled in Art. Most Cited Cases

**Patents 291 36.1(1)**

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k36 Weight and Sufficiency
291k36.1 Secondary Factors Affecting Invention or Obviousness
291k36.1(1) k. In General. Most Cited Cases

**Patents 291 36.2(1)**

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k36 Weight and Sufficiency
291k36.2 Commercial Success
291k36.2(1) k. In General. Most Cited Cases
Factor court considers when making patent obviousness inquiry include: (1) scope and content of prior art; (2) differences between claims and prior art; (3) level of ordinary skill in pertinent art; and (4) secondary considerations, which include objective evidence of nonobviousness such as long-felt but unsolved need which invention addresses, failure of others to formulate invention, and commercial success of invention. 35 U.S.C.A. § 103(a).

**[9] Patents 291 16.5(1)**

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16.5 State of Prior Art and Advancement Therein
291k16.5(1) k. In General. Most Cited Cases
In order for multiple prior art references to collectively render patent invalid as obvious, there must be reason, suggestion, or motivation in prior art that would lead one of ordinary skill in art to combine references, and that would also suggest reasonable likelihood of success. 35 U.S.C.A. § 103(a).

**[10] Patents 291 323.2(3)**

291 Patents
291XII Infringement
291XII(C) Suits in Equity
291k323 Final Judgment or Decree
291k323.2 Summary Judgment
291k323.2(3) k. Particular Cases. Most Cited Cases
Issues of material fact as to level of ordinary skill in art and

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motivation to combine precluded summary judgment on question of whether patent for method of analyzing polynucleotide sequences, calling for attachment of known oligonucleotides to impermeable surface, was rendered obvious by combination of prior art calling for attachment of known oligonucleotides to permeable support surface and prior art calling for attachment of unknown polynucleotides to impermeable support surface. 35 U.S.C.A. § 103(a).

**[11] Patents 291 ⚷16(3)**

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16 Invention and Obviousness in General
291k16(3) k. View of Person Skilled in Art. Most Cited Cases

**Patents 291 ⚷16.5(1)**

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16.5 State of Prior Art and Advancement Therein
291k16.5(1) k. In General. Most Cited Cases

Factors court considers in determining ordinary level of skill in art, for purpose of patent obviousness inquiry, include: (1) type of problems encountered in art; (2) prior art solutions to those problems; (3) rapidity with which innovations are made; (4) sophistication of technology; and (5) educational level of active workers in field. 35 U.S.C.A. § 103(a).

**[12] Patents 291 ⚷26(1)**

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k26 Combination
291k26(1) k. In General. Most Cited Cases

Suggestion to combine prior art references, as required for finding of patent obviousness, may be found in explicit or implicit teachings within references themselves, from ordinary knowledge of those skilled in art, or from nature of problem to be solved; in any event, though, there must be evidence that skilled artisan, confronted with same problems as inventor and with no knowledge of claimed invention, would select elements from cited prior art references for combination in manner claimed. 35 U.S.C.A. § 103(a).

**[13] Patents 291 ⚷229**

291 Patents
291XII Infringement
291XII(A) What Constitutes Infringement
291k228 Patents for Processes
291k229 k. Identity in General. Most Cited Cases

Claim in patent for method of analyzing polynucleotide sequences, calling for monomer by monomer synthesis of oligonucleotides on substrate, was not infringed by accused method which deposited fully-formed oligonucleotides on substrate.

**[14] Patents 291 ⚷101(2)**

291 Patents
291IV Applications and Proceedings Thereon
291k101 Claims
291k101(2) k. Construction in General. Most Cited Cases

**Patents 291 ⚷101(11)**

291 Patents
291IV Applications and Proceedings Thereon
291k101 Claims
291k101(11) k. Process or Method Claims. Most Cited Cases

Patent claim term "comprises" is open-ended and does not exclude additional, unrecited elements or method steps.

**[15] Patents 291 ⚷229**

291 Patents
291XII Infringement
291XII(A) What Constitutes Infringement
291k228 Patents for Processes
291k229 k. Identity in General. Most Cited Cases

Patent for method of analyzing polynucleotide sequences by applying them to array of known oligonucleotides, fixed on impermeable surface, under hybridization conditions was infringed by accused method of gene expression analysis, even though accused method interposed permeable gel between oligonucleotides and impermeable substrate; claim was not limited to direct

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attachment of oligonucleotides to impermeable surface.

**[16] Patents 291 ⚷229**

291 Patents
291XII Infringement
291XII(A) What Constitutes Infringement
291k228 Patents for Processes
291k229 k. Identity in General. Most Cited Cases

Patent for method of analyzing polynucleotide sequences by applying them to array of known oligonucleotides and observing pattern of hybridization was infringed by accused method of gene expression analysis, under which hybridization expression patterns on test and control arrays were compared.

**[17] Patents 291 ⚷259(1)**

291 Patents
291XII Infringement
291XII(A) What Constitutes Infringement
291k259 Contributory Infringement; Inducement
291k259(1) k. In General. Most Cited Cases

Whether directly infringing or not, party may still be liable for inducement or contributory infringement of method claim if it sells infringing devices to customers who use them in way that directly infringes method claim. 35 U.S.C.A. § 271(b, c).

**[18] Patents 291 ⚷259(1)**

291 Patents
291XII Infringement
291XII(A) What Constitutes Infringement
291k259 Contributory Infringement; Inducement
291k259(1) k. In General. Most Cited Cases

Direct patent infringement is prerequisite to liability for inducing infringement. 35 U.S.C.A. § 271(b).

**[19] Patents 291 ⚷259(1)**

291 Patents
291XII Infringement
291XII(A) What Constitutes Infringement
291k259 Contributory Infringement; Inducement
291k259(1) k. In General. Most Cited Cases

**Patents 291 ⚷312(8)**

291 Patents
291XII Infringement
291XII(C) Suits in Equity
291k312 Evidence
291k312(3) Weight and Sufficiency
291k312(8) k. Participation, Intent, and Contributory Infringement. Most Cited Cases

Patent infringer cannot be held liable for inducing infringement unless inducement is intentional; such intent can be imputed to defendant who should have known that its actions would induce actual infringement, and can be established through circumstantial evidence. 35 U.S.C.A. § 271(b).

**[20] Patents 291 ⚷259(1)**

291 Patents
291XII Infringement
291XII(A) What Constitutes Infringement
291k259 Contributory Infringement; Inducement
291k259(1) k. In General. Most Cited Cases

Manufacturer of gene expression analysis device induced its customers' direct infringement of patented method of analyzing polynucleotide sequences; manufacturer instructed customers on how to use device in infringing manner. 35 U.S.C.A. § 271(b).

**[21] Patents 291 ⚷259(1)**

291 Patents
291XII Infringement
291XII(A) What Constitutes Infringement
291k259 Contributory Infringement; Inducement
291k259(1) k. In General. Most Cited Cases

Liability for contributory patent infringement is premised on theory of joint tortfeasance, wherein one who intentionally causes, or aids and abets, commission of tort by another is jointly and severally liable with primary tortfeasor. 35 U.S.C.A. § 271(c).

**[22] Patents 291 ⚷259(1)**

291 Patents
291XII Infringement
291XII(A) What Constitutes Infringement

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291k259 Contributory Infringement; Inducement
291k259(1) k. In General. Most Cited Cases
Elements of contributory infringement claim are: (1) offer to sell, sale, or import; (2) component or material for use in patented process constituting material part of invention; (3) knowledge by defendant that component is especially made or especially adapted for use in infringement of such patent; (4) component is not staple or article suitable for substantial noninfringing use; and (5) actual or necessary direct infringement by defendant's customer. 35 U.S.C.A. § 271(c).

**[23] Patents 291 259(1)**

291 Patents
291XII Infringement
291XII(A) What Constitutes Infringement
291k259 Contributory Infringement; Inducement
291k259(1) k. In General. Most Cited Cases
Manufacturer of gene expression analysis device was contributorily liable for its customers' direct infringement of patented method of analyzing polynucleotide sequences; manufacturer's device had no substantial noninfringing use. 35 U.S.C.A. § 271(c).

**Patents 291 328(2)**

291 Patents
291XIII Decisions on the Validity, Construction, and Infringement of Particular Patents
291k328 Patents Enumerated
291k328(2) k. Original Utility. Most Cited Cases
4,994,373. Cited as Prior Art.

**Patents 291 328(2)**

291 Patents
291XIII Decisions on the Validity, Construction, and Infringement of Particular Patents
291k328 Patents Enumerated
291k328(2) k. Original Utility. Most Cited Cases
6,054,270. Infringed in Part.

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**MEMORANDUM OPINION**

JORDAN, District Judge.

**I. INTRODUCTION**

This is a patent infringement case. Presently before me are several motions filed by plaintiff, Oxford Gene Technology Limited ("OGT"), and defendant, Mergen Limited ("Mergen"). Those filed by OGT include a Motion for Partial Summary Judgment of Patent Validity and Enablement (Docket Item ["D.I."] 177; the "Motion for Validity"), a Motion for Partial Summary Judgment of Infringement (D.I. 179; the "Motion for Infringement"), and a Motion to Strike Mergen's Newly Identified Non-Enablement Defense (D.I. 202; the "Motion to Strike"). Those filed by Mergen include a Motion for Summary Judgment of Invalidity of the Asserted Claims of U.S. Patent No. 6,054,270 (the " '270 patent") (D.I. 181; the "Motion for Invalidity"), a Motion for Summary Judgment of Non-Infringement of Claims 1, 9 and 10 of U.S. Patent No. 6,054,270 (D.I. 185; the "Motion for Non-Infringement"), and a Motion for Summary Judgment of Invalidity of Claim 1 of U.S. Patent No. 6,054,270 (D.I. 190; the "Motion for Invalidity of Claim 1").

Jurisdiction is proper under 28 U.S.C. §§ 1331 and 1338. For the reasons that follow, OGT's Motion for Validity will be denied, OGT's Motion for Infringement will be granted with respect to claims 9 and 10 and denied with respect to claim 1,[FN1] OGT's Motion to Strike will be denied as moot,[FN2] Mergen's Motion for Invalidity will be denied, Mergen's Motion for Non-Infringement will be granted with respect to claim 1 and denied with respect to claims 9 and 10,[FN3] and Mergen's Motion for Invalidity of Claim 1 will be denied without prejudice.[FN4]

FN1. Based on my construction of claim 1, OGT has stipulated to: "(a) the denial of OGT's Motion for Partial Summary Judgment of Infringement (D.I. 179, 180) with respect to claim I only ... and (b) the grant of Mergen's Motion for Summary Judgment of Non-infringement (D.I. 185, 186) with respect to claim 1 only ...." (D.I. 240.)

FN2. Based on OGT's stipulation regarding claim

1 of U.S. Patent No. 6,054,270 (the " '270 patent") (D.I. 240; *see* footnote 1), OGT's Motion to Strike is denied as moot because it relates only to the issue of the validity of claim 1.

FN3. Based on OGT's stipulation regarding claim 1 of the '270 patent (D.I. 240; *see* footnote 1), Mergen's Motion for Non-Infringement will be granted with respect to claim 1.

FN4. Based on OGT's stipulation regarding claim 1 of the '270 patent (D.I. 240; *see* footnote 1), I exercise my discretion to dismiss without prejudice Mergen's counterclaim of declaratory judgment of invalidity with respect to claim 1. *See* *Liquid Dynamics Corp. v. Vaughan Co., Inc.*, 355 F.3d 1361, 1371 (Fed.Cir.2004) ("A district court judge faced with an invalidity counterclaim challenging a patent that it concludes was not infringed may either hear the claim or *dismiss it without prejudice,* subject to review only for abuse of discretion.") (internal citation omitted) (emphasis added).

***448 II. BACKGROUND**

The background related to the '270 patent is set forth in my November 16, 2004 Order and Opinion (D.I. 242, 243) and will not be repeated here. Claim 1 of the patent states, as follows:

1. A method of making an array of oligonucleotides, which comprises:

attaching a plurality of oligonucleotides to an impermeable surface of a support, the oligonucleotides having different predetermined sequences and being attached at different known locations on the surface of the support through a computer-controlled printing device.

('270 patent, col. 15, ll. 47-53.) I have construed "through a computer-controlled printing device" to mean "through a computer-controlled printing device using monomer by monomer synthesis of oligonucleotides." (D.I. 238 at 14-18.) In short, claim one covers only *in situ* synthesis of oligonucleotides.
Claim 9 reads as follows:

9. A method of analysing a polynucleotide, which method comprises:

applying a labelled polynucleotide to be analysed or fragments thereof to an array of oligonucleotides under hybridisation conditions, wherein the array comprises a support having an impermeable surface to which a plurality of oligonucleotides having different predetermined sequences are attached to different known regions on the surface, and

analysing the polynucleotide by observing the regions where the polynucleotide or fragment thereof hybridizes and the regions where the polynucleotide or fragment thereof does not hybridize.

('270 patent, col. 16, ll. 44-56.) I have construed the terms of claim 9 as follows:

| CLAIM TERM | MEANING |
|---|---|
| "to an array of oligonucleotides" | "to two or more oligonucleotide sequences located at different regions on a singlesupport" |
| "under hybridisation conditions" | "under conditions suitable for hybridization" |
| "a support having an impermeable surface" | "a solid having a non-porous surface that does not permit diffusion through itssubstance" |

| | |
|---|---|
| "are attached" | "are affixed" |
| "by observing the regions where the polynucleotide or fragment thereof hybridizes and the regions where the polynucleotide orfragment thereof does not hybridize" | "by observing the regions where the polynucleotide or fragment thereof hybridizes and the regions where the polynucleotide orfragment thereof does not hybridize" |

*Oxford Gene*, 2004 WL 2211971, at *9-*11.

Claim 10 reads as follows:

10. A method of comparing polynucleotide sequences, which method comprises:

applying the polynucleotides to an array of oligonucleotides under hybridizing conditions, wherein the oligonucleotides have different predetermined sequences and are attached at different known locations on an impermeable surface of a support, and

observing the differences between the patterns of hybridisation.

***449** ('270 patent, col. 16, ll. 57-65.) I gave the claim terms which also appear in claim 9 the same construction I gave them with respect to claim 9. I determined that the only new limitation, namely "observing the differences between the patterns of hybridisation," can be understood in accordance with its plain and ordinary meaning and requires no further construction. *Id.* at *12-*13.

**III. STANDARD OF REVIEW**

Pursuant to Federal Rule of Civil Procedure 56(c), a party is entitled to summary judgment if a court determines from its examination of "the pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any," that there are no genuine issues of material fact and that the moving party is entitled to judgment as a matter of law. In determining whether there is a triable issue of material fact, a court must review the evidence and construe all inferences in the light most favorable to the non-moving party. *Goodman v. Mead Johnson & Co.*, 534 F.2d 566, 573 (3d Cir.1976). However, a court should not make credibility determinations or weigh the evidence. *Reeves v. Sanderson Plumbing Prods., Inc.*, 530 U.S. 133, 150, 120 S.Ct. 2097, 147 L.Ed.2d 105 (2000). To defeat a motion for summary judgment, Rule 56(c) requires that the non-moving party "do more than simply show that there is some metaphysical doubt as to the material facts." *Matsushita Elec. Indus. Co., Ltd. v. Zenith Radio Corp.*, 475 U.S. 574, 586-87, 106 S.Ct. 1348, 89 L.Ed.2d 538 (1986) (internal citation omitted). The non-moving party "must set forth specific facts showing that there is a genuine issue for trial." Fed.R.Civ.P. 56(c). "Where the record taken as a whole could not lead a rational trier of fact to find for the non-moving party, there is no genuine issue for trial." *Matsushita Elec. Inds. Co., Ltd.*, 475 U.S. at 587, 106 S.Ct. 1348 (internal citation omitted). Accordingly, a mere scintilla of evidence in support of the non-moving party is insufficient for a court to deny summary judgment. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 252, 106 S.Ct. 2505, 91 L.Ed.2d 202 (1986).

A. Patent Validity

[1][2] When a party challenges a patent's validity, the starting point for analyzing that challenge is the statutory presumption of validity. *See*35 U.S.C. § 282 ("A patent shall be presumed valid."). Accordingly, "[t]he burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity." *Id.* Invalidity must be shown by clear and convincing evidence. *Robotic Vision Sys. v. View Eng'g, Inc.*, 189 F.3d 1370, 1377 (Fed.Cir.1999). This presumption of validity is never weakened, and the burden of proving invalidity does not shift from the party asserting invalidity. *Imperial Chem. Indus., PLC v. Danbury Pharmacal, Inc.*, 745 F.Supp. 998, 1004 (D.Del.1990) (citing *ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1574-75 (Fed.Cir.1984) (other citations omitted)). The burden of going forward with evidence rebutting invalidity may shift to the patentee only after the party asserting invalidity has demonstrated a legally sufficient *prima facie* case of invalidity. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 291 (Fed.Cir.1985) (internal citations omitted). If the party asserting invalidity has established a legally sufficient case of invalidity, the court then examines all of the evidence of

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invalidity together with all of the evidence rebutting invalidity, and determines whether there is clear and convincing evidence of invalidity. Id. at 291-92.

B. Infringement

[3][4] A patent infringement analysis involves two steps: claim construction and ***450** then the application of the construed claim to the accused process or product. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed.Cir.1995) (en banc), *aff'd*, 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996). The first step, claim construction, has been held to be purely a matter of law. *See Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1454 (Fed.Cir.1998) (en banc). The second step, application of the claim to the accused product, is a fact-specific inquiry. *See Kustom Signals, Inc. v. Applied Concepts, Inc.*, 264 F.3d 1326, 1332 (Fed.Cir.2001) (Patent infringement, "whether literal or under the doctrine of equivalents, is a question of fact."). Summary judgment is appropriate in patent infringement suits when it is apparent that only one conclusion regarding infringement could be reached by a reasonable jury. *See Telemac Cellular Corp. v. Topp Telecom, Inc.*, 247 F.3d 1316, 1323 (Fed.Cir.2001).

**IV. DISCUSSION**

A. VALIDITY FN5 OF CLAIMS 9 AND 10

> FN5. As noted, *supra* note 1, I have chosen to decline an examination of the validity of claim 1, since the parties have agreed that, under my construction of that claim, Mergen does not infringe that claim.

1. Anticipation

[5] Mergen moves for summary judgment on the basis that claims 9 and 10 of the '270 patent are invalid as anticipated by European Patent Application No. 235 726 A2 (the " '726 application"). (D.I. 182 at 14-16.) OGT moves for summary judgment that claims 1, 9, and 10 are not anticipated and therefore, not invalid. (D.I. 178 at 11-13.) Anticipation requires that each and every element of the claimed invention be disclosed in a single prior art reference. *In re Paulsen*, 30 F.3d 1475, 1478-79 (Fed.Cir.1994). In other words, if any claimed element is missing from the prior art reference, it cannot anticipate the claimed invention. *Kloster Speedsteel AB v. Crucible Inc.*, 793 F.2d 1565, 1571 (Fed.Cir.1986) (citation omitted), *overruled on other grounds by Knorr-Bremse Systeme Fuer Nutzfahrzeuge GmbH v. Dana Corp.*, 383 F.3d 1337 (Fed.Cir.2004).

[6] Even in considering the evidence in the light most favorable to Mergen, there is no material issue of fact to preclude a finding on summary judgment that the '726 application does not anticipate claims 9 and 10 of the '270 patent. A common limitation of claims 9 and 10 is that each requires the support to which the oligonucleotides are attached to have an impermeable surface. Claim 9 states: "... wherein the array comprises a support having an *impermeable surface*...."('270 patent, col. 16, ll. 48-49 (emphasis added).) Claim 10 states: "... on an *impermeable surface* of a support ...."('270 patent, col. 16, ll. 62-63 (emphasis added).) The '726 application, however, does not disclose an impermeable surface of a support, and therefore cannot anticipate. Additional evidence makes this perfectly clear.

First, Mergen admits that "... the '726 application does not specifically disclose impermeable surfaces ...." (D.I. 217 at 16.) Second, while Mergen argues that impermeable surfaces were somehow inherent in the "solid sheets" disclosed in the '726 application, neither OGT's expert, Dr. Vrana, nor Mergen's own expert, Dr. Purdue, agreed. (*See* D.I. 151, Vrana Validity Report at 5-7; D.I. 193, Ex. 5, 186 at 14:01:03 12-4:01:37 25, Dep. Dr. Perdue, July 14, 2004.) On the contrary, the '726 application describes the method of "blotting," which requires the use of permeable ***451** surfaces, as expressly disclosed in that reference. (D.I. 151, Vrana Validity Report at 5-7.) Third, the only evidence offered by Mergen in support of its Motion for Invalidity based on anticipation is the deposition testimony of Dr. Vrana, OGT's validity expert, who concluded that no prior art reference anticipated the patent-in-suit. When asked whether the '726 application disclosed impermeable supports, he replied, "I couldn't, I couldn't say that." (D.I. 218, Ex. G at 280.) In addition, Mergen's own expert, Dr. Purdue admitted in deposition testimony that in his opinion, none of the prior art references invalidates any of the claims.

Q: ... Do you have opinions as to whether or not any prior art reference invalidates any claim of the '270 patent for any reason?

...

A: You're asking me whether right now I believe that a

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single piece of prior art invalidates any of the claims?

Q: That's correct, the anticipation as a test....

A: We've covered this ground before, and none of them do on their own.

(D.I. 193, Ex. 5 at 186, 14:01:03 12-4:01:37 25, Dep. Dr. Purdue, July 14, 2004.) Finally, Mergen's own concluding argument on this issue sets forth premises that admit the lack of anticipation. Mergen argued: "If the Court construes claims 9 and 10 to include arrays where oligonucleotides are attached to a surface of a support that is *permeable,* and via a method of attachment that does not require *in situ* synthesis, then the '726 application discloses each and every element of the invention claimed in claims 9 and 10 of the '270 patent...." (D.I. 182 at 16 (emphasis added).) Thus, even Mergen concludes that the court would have to find that claims 9 and 10 included a permeable surface to find that the '726 application anticipates. But, of course, claims 9 and 10 contain the opposite limitation, an impermeable surface of a support.

Because the '726 application does not anticipate the '270 patent, Mergen's Motion for Invalidity with regard to anticipation will be denied. And while OGT's Motion for Validity cannot be granted on this basis alone,[FN6] Mergen will not be permitted to argue that the '270 patent is invalid because it is anticipated by the '726 application.

FN6. To say a patent is not anticipated does not mean that there can be no other basis for invalidity. In this case, there are other arguments for invalidity which cannot be resolved on summary judgment. (*See infra* section IV.A.2.)

2. Obviousness

[7][8][9] Mergen moves for summary judgment on the basis that claims 1, 9, and 10 of the '270 patent are invalid for obviousness. (D.I. 182 at 19-21.) OGT moves for summary judgment that these three claims are not obvious and therefore, not invalid. (D.I. 178 at 12-23.) A patent is invalid for obviousness under 35 U.S.C. § 103, "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). The ultimate determination of obviousness is a question of law based on underlying factual inquiries. *See Rockwell Int'l Corp. v. United States,* 147 F.3d 1358, 1362 (Fed.Cir.1998) (citation omitted). These inquiries include determining (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the pertinent art; and (4) secondary considerations,***452** which include objective evidence of nonobviousness such as a long-felt but unsolved need which the invention addresses, the failure of others to formulate the invention, and the commercial success of the invention. *Graham v. John Deere Co. of Kansas City,* 383 U.S. 1, 17-18, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966).[FN7] The existence of each element of a claim in the prior art, however, does not, by itself, demonstrate obviousness. *See Moore N. Am., Inc. v. Poser Bus. Forms, Inc.,* No. Civ.A. 97-712-SLR, 2001 WL 253117, at *5 (D.Del. Mar.8, 2001). Instead, there must be a "reason, suggestion, or motivation in the prior art that would lead one of ordinary skill in the art to combine the references, and that would also suggest a reasonable likelihood of success." *Smiths Indus. Med. Sys., Inc. v. Vital Signs, Inc.,* 183 F.3d 1347, 1356 (Fed.Cir.1999) (internal citation omitted).

FN7. A district court cannot make a proper obviousness determination without undertaking an analysis under *Graham. See Greenwood v. Hattori Seiko Co., Ltd.,* 900 F.2d 238, 241 (Fed.Cir.1990) ("Since the proper *Graham* analysis was not made by the district court, the summary judgment of obviousness under 35 U.S.C. § 103 must be vacated."); *Loctite Corp. v. Ultraseal Ltd.,* 781 F.2d 861, 872-73 (Fed.Cir.1985) ( "In patent cases, the need for express *Graham* findings takes on an especially significant role because of an occasional tendency of district courts to depart from the *Graham* test ...."), *overruled on other grounds by Nobelpharma AB v. Implant Innovations, Inc.,* 141 F.3d 1059 (Fed.Cir.1998).

In its Motion for invalidity, Mergen makes two arguments regarding obviousness as it relates to claims 9 and 10 of the '270 patent. The first is that claims 9 and 10 are obvious in light of the '726 application in combination with what would have been known by one of ordinary skill in the art, specifically the alleged common knowledge of using glass supports for hybridization. (D.I. 183 at 14-16.) Mergen's second argument is that claims 9 and 10 are obvious in light of the '726 application in combination with the '373 patent. (*Id.* at 19-21.) As support for both arguments,

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Mergen relies on Dr. Purdue's Declaration, in which he restates the opinions expressed in his expert report. (*See* D.I. 182 at 16 (referring to Dr. Purdue's Declaration (D.I. 183) at ¶ 7 for the proposition that it was well known in the field to use glass supports for hybridization); D.I. 182 at 20 (referring to Dr. Purdue's Declaration (D.I. 183) at ¶¶ 8-9 for the proposition that the '373 patent in combination with the '726 application renders claims 1, 9, and 10 obvious to one skilled in the art).)

[10] Because I have already concluded that Dr. Purdue's opinion lacked sufficient support for the proposition that one of ordinary skill in the art would know to use glass supports for hybridization (D.I. 242 at 1; D.I. 243 at 11-13), Mergen's first argument must fail. Therefore, Mergen's only obviousness argument with evidentiary support is that the '270 patent is obvious based on the '726 application in view of the '373 patent.

a. The Scope and Content of the Prior Art

A proper inquiry into the first *Graham* factor should focus on the claims in suit, the art the PTO applied to the claims, and the nature of the problem confronting the inventor. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 449 (Fed.Cir.1986). In this case, there are two prior art references that must be considered: the '726 application and the '373 patent.[FN8]

FN8. Neither party disputes that both references constitute prior art under 35 U.S.C. § 102. The '726 application was filed in Europe on February 24, 1987. (D.I. 184, Ex. 3 at PR 000241, '726 application at 1.) The '373 patent was filed on July 20, 1989 as a continuation, and claims a priority date back to at least May 9, 1985. (D.I. 184, Ex. 4 at PUR 000232, '373 patent at 1.)

***453** The '726 application teaches a method of making an oligonucleotide array that includes immobilizing or attaching one or more oligonucleotides of known sequence to a solid support at different known locations on its surface. It also discusses what is now called the "reverse dot blot" technique. In this technique, as taught by the '726 application, oligonucleotide probes of known sequence are attached to a support surface by "blotting" them to the surface and are then hybridized with a liquid sample containing labeled polynucleotides of unknown sequence. It teaches a variety of approaches for attaching oligonucleotide probes to a support, including both non-covalent and covalent attachment to permeable supports such as nitrocellulose and nylon. It also teaches to observe the locations where hybridization has occurred, by observing the labeled areas. This method can be used to detect certain genetic disorders. ('726 application; D.I. 212, Ex. A at 6, Expert Report of Dr. Purdue; D.I. 193, Ex. 8 at 4, Rebuttal Expert Report of Dr. Vrana.)

The '373 patent teaches a method of analyzing polynucleotide sequences by attaching the polynucleotides to a solid support, and hybridizing them with labeled oligonucleotide or polynucleotide probes of known sequence. It teaches that non-porous and transparent supports, such as glass, are preferred over porous materials, such as nitrocellulose filters. ('373 patent, col. 5, ll. 46-52.) It discloses a product for performing the disclosed detection of a polynucleotide sequence, which contains a portion for retaining a fluid in which the immobilized polynucleotide sequence is located. According to the '373 patent, the portion of the product for containing the fluid is preferably a well, a tube, or a cuvette. Any resulting hybridization then occurs within this fluid. ('373 patent; D.I. 212, Ex. A at 7-8, Expert Report of Dr. Purdue; D.I. 193, Ex. 8 at 17-18, Rebuttal Expert Report of Dr. Vrana.)

b. The Differences Between the Claimed Invention and the Prior Art

With respect to this second *Graham* factor, the court must view the claimed invention *as a whole*. *Bausch & Lomb*, 796 F.2d at 449 (citation omitted) (emphasis in original); *see also* *Applied Materials, Inc. v. Advanced Semiconductor Materials Am., Inc.*, 98 F.3d 1563, 1570 (Fed.Cir.1996) ("[T]he determination of obviousness, *vel non*, requires that all the evidence be considered together.").

Although Mergen argues that the '726 application on its own teaches all of the limitations of claims 9 and 10 of the '270 patent, (D.I. 217 at 21)-an argument I have already rejected (*see supra* section IV.A.1.)-Mergen also argues in the alternative that the '726 application teaches all of the limitations of those claims except an impermeable surface. (D.I. 217 at 21.) OGT apparently does not disagree with that alternative assertion, and neither do I.

Turning then to the only other prior art source available to Mergen to demonstrate the use of an impermeable support for hybridization, I review the '373 patent. There are two differences between the '373 patent and the claimed invention as a whole. The first, is that the '373 patent

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teaches a method of analysis involving attachment of unknown polynucleotides to a solid support followed by hybridization with labeled oligonucleotide or polynucleotide probes of known sequence. ('373 patent, col 1, ll. 25-45, col. 5, ll. 15-67.) This ***454** method was known as a "dot blot" technique. (*See* D.I. 193, Ex. 8 at 4, Rebuttal Expert Report of Dr. Vrana.) The invention disclosed in the patent-in-suit, on the other hand, teaches the "reverse dot blot" technique, in which the known oligonucleotide probes are attached to the surface of an impermeable support, rather than the unknown polynucleotides being attached. The second difference is that the '373 patent teaches that the hybridization be detectable in solution and that, therefore, the analysis be performed on a solid support that "is desirably a well, a tube, or a cuvette." ('373 patent, col. 7, ll. 49-50.) The invention described in the '270 patent does not require the sample to be in a solution for detection and therefore does not utilize wells, tubes, or cuvettes, but utilizes instead simply "an array of oligonucleotides." FN9

FN9. "An array of oligonucleotides" was construed to mean "two or more oligonucleotide sequences located at different regions on a single support." *Oxford Gene,* 2004 WL 2211971, at *4, *10, *12.

The focus of Mergen's argument is that the '373 patent teaches an impermeable surface of support, the one claim limitation that the '726 application is missing. (D.I. 217 at 21-22.) In the Notice of Allowability for the '270 patent, the examiner stated two features of the invention that the '373 patent did not teach: "monomer by monomer synthesis of oligonucleotides on a surface ... [and] the hybridization assay practice of utilizing an array of different oligonucleotide probes on a single surface." (D.I. 193, Ex. 8, Dr. Vrana's Rebuttal Expert Report, Ex. F at 4.) FN10 Because claims 9 and 10 were not limited to monomer by monomer synthesis (*see Oxford Gene,* 2004 WL 2211971, at *14), the only remaining difference is that the '373 patent did not utilize "an array of different oligonucleotide probes on a single surface." (D.I. 193, Ex. 8, Dr. Vrana's Rebuttal Report, Ex. F. at 4.) That difference was apparently noted because the invention practices the "reverse dot-blot" technique while the '373 patent teaches the "dot-blot" technique, the examiner having observed that the '373 patent taught that it was the unknown polynucleotides which were attached to the surface, not the known oliogonucleotide or polynucleotide probes.

FN10. It is not entirely clear whether the examiner's statements relate to all of the allowed claims. To the best of my understanding, however, they do relate at least to claims 9 and 10, as well as to claim 1.

c. The Level of Ordinary Skill in the Art

[11] The *Graham* test for obviousness of a claimed invention "includes a factual determination of the level of ordinary skill in the art." *Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc.,* 807 F.2d 955, 962 (Fed.Cir.1986). Without this information, the court cannot properly assess obviousness because the critical question is whether a claimed invention would have been obvious, at the time it was made, to one of ordinary skill in the art. *Id.*"The person of ordinary skill is a hypothetical person who is presumed to be aware of all the pertinent prior art." FN11 *Id.* (internal citation omitted). Factors that may be considered in determining the level of skill include: "the type of problems encountered in the art; prior art solutions to those problems; rapidity with which ***455** innovations are made; sophistication of the technology; and educational level of active workers in the field." *Id.* (internal citation omitted).

FN11. At least one commentator has asserted that, "in the context of a summary judgment motion, the trial judge is really resolving the question by reference to the skill of the layperson, which is, except in rare circumstances, the most favorable view for the patentee." Robert L. Harmon, Patents and the Federal Circuit § 4.3, at 168 (6th ed.2003) (citing *Union Carbide Corp. v. Am. Can Co.,* 724 F.2d 1567 (Fed.Cir.1984)).

Although neither party made any effort to apply these factors, each has proposed a level of ordinary skill in the art. OGT's proposal is that "a person of ordinary skill in the art at the time of the invention (1988) would have a Ph.D. degree in Biomedical Sciences, Biochemistry, or a relevant sub-discipline of Biology (such as Molecular Biology) or Chemistry, with a few years of experience in or exposure to studies of genomics, gene expression, or nucleic acid hybridization." (D.I. 194, Ex. 3 at 10, Expert Report of Dr. Vrana; D.I. 178 at 15; D.I. 193, Ex. 8 at 25, Rebuttal Expert Report of Dr. Vrana (referring to Dr. Vrana's Expert Report).) Mergen's proposal is that a person of ordinary skill in the art would be one "who had an advanced degree in science working in the field of molecular biology, and/or one with a bachelors degree who has done laboratory work in molecular biology for several years." (D.I. 212, Ex. A at

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5, Expert Report of Dr. Purdue.) The parties have merely provided assertions of the level of ordinary skill in the art without explaining the bases for their conclusions. Therefore, Mergen has not satisfied its burden to prove that there is no genuine issue of material fact as to who qualifies as a person of ordinary skill in the art pertaining to the analysis of polynucleotides. Indeed, Mergen has failed to establish even a *prima facie* case of obviousness that would shift the burden of going forward with evidence to OGT.

d. Motivation to Combine

There are also genuine issues of material fact as to whether one of ordinary skill in the art would have been motivated to combine the teachings of the '373 patent and the '726 application. Mergen's only argument in support of finding the necessary motivation is that both references are "in the same field of endeavor and represent different variations of similar experimental techniques involving oligonucleotide and/or polynucleotide hybridization for the purposes of polynucleotide sequence analysis." (D.I. 182 at 20.)

[12] "[T]he suggestion to combine may be found in explicit or implicit teachings within the references themselves, from the ordinary knowledge of those skilled in the art, or from the nature of the problem to be solved." *Ecolochem, Inc. v. Southern Cal. Edison Co.*, 227 F.3d 1361, 1375 (Fed.Cir.2000) (quoting *WMS Gaming, Inc. v. Int'l Game Tech.*, 184 F.3d 1339, 1355 (Fed.Cir.1999)). There still, however, must be evidence that "a skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." *Id.* (quoting *In re Rouffet*, 149 F.3d 1350, 1357 (Fed.Cir.1998)); *see also In re Werner Kotzab*, 217 F.3d 1365, 1371 (Fed.Cir.2000) ("[A] rejection cannot be predicated on the mere identification ... of individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed."). Here, Mergen has not presented any evidence beyond the assertion of its expert that there would have been a motivation to combine. OGT, of course, denies that one of ordinary skill in the art would have selected these components for combination in the manner claimed. (D.I. 178 at 14-15; D.I. 231 at 11-13.) Therefore, a genuine issue of material fact remains on this issue.

***456** e. Secondary Considerations

Because Mergen has failed to establish a *prima facie* case of invalidity of the '270 patent based on obviousness by clear and convincing evidence, and because it is not until "a *prima facie* case has been established, [that] the burden shifts to the patentee to go forward with rebuttal evidence showing facts supporting nonobviousness," *Ashland Oil*, 776 F.2d at 291-92 (citing *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1573 (Fed.Cir.1985); *accord*, *In re Piasecki*, 745 F.2d 1468, 1472 (Fed.Cir.1984)) any discussion of secondary considerations at this stage would be premature.

The same factual issues that require the denial of Mergen's Motion for Invalidity also require the denial of OGT's Motion for Validity. However, the motions practice on this point has had the effect of demonstrating that Mergen may only challenge the validity of the '270 patent on the issue of obviousness based on the '726 application in view of the '373 patent.

B. INFRINGEMENT

1. Direct Infringement

OGT has moved for summary judgment that Mergen literally infringes claims 1, 9, and 10 of the '270 patent. (D.I. 180 at 1.) OGT argues that Mergen directly infringes claims 1, 9, and 10 of the '270 patent, and indirectly infringes claims 9 and 10. (*Id.*) Mergen has moved for summary judgment of noninfringement of claims 1, 9, and 10 of the '270 patent. (D.I. 186 at 1.) Determining whether an accused product infringes is a two-step process. *Markman*, 52 F.3d at 976. The first step, construing the disputed claim terms, has already occurred in this case. *Oxford Gene*, 2004 WL 2211971. I now proceed to step two, a "comparison of the claim to the accused device, [which] requires a determination that every claim limitation or its equivalent be found in the accused device [or process]." *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1370 (Fed.Cir.2002) (citing *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 29, 117 S.Ct. 1040, 137 L.Ed.2d 146 (1997)).

In order for OGT to succeed on summary judgment of literal infringement, it must prove that Mergen practices each and every claim limitation of each asserted claim. Mergen, however, only has to prove that it does not practice any one of the limitations and OGT's Motion for

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Infringement must be denied. Mergen argues that its accused products and services do not infringe the asserted claims of the '270 patent for four reasons:

(1) Mergen's presynthesized oligonucleotides are attached to a permeable polyacrylamide matrix or gel coating on a glass slide, and are not attached to the impermeable surface of a support, as required by the asserted claims of the '270 patent under either parties' proposed claim construction[;] (2) Mergen uses a deposition method to deposit fully formed oligonucleotides on a coated slide to make its microarray, whereas the '270 patent discloses and the asserted claims require an *in situ* or monomer by monomer synthesis method of making microarrays[;] (3) Mergen's microarrays are and can only be used for gene expression analysis, and not for analysis of polynucleotide sequences, as required by claims 9 and 10 of the '270 patent[; and] (4)[t]he hybridization conditions used in Mergen's methods differ significantly from those disclosed in the '270 patent and required by claims 9 and 10.

(D.I. 186 at 1-2.) With those arguments in mind, I review each of the claims in dispute.

a. Claim 1

[13] Claim 1 is actually no longer in dispute. Based on my construction of ***457** claim 1, OGT has stipulated to: "(a) the denial of OGT's Motion for Partial Summary Judgment of Infringement (D.I. 179, 180) with respect to claim 1 only ... and (b) the grant of Mergen's Motion for Summary Judgment of Non-infringement (D.I. 185, 186) with respect to claim 1 only ...." (D.I. 240.) In claim 1, I construed the claim term "through a computer-controlled printing device" to mean "through a computer-controlled printing device using monomer by monomer synthesis of oligonucleotides." (*See* Background, section II; note 1.) This construction limits the coverage of claim 1 to the *in situ* method of synthesis which OGT admits Mergen does not practice literally or under the doctrine of equivalents. (D.I. 240 at 1.) Therefore, with regard to claim 1, OGT's Motion for Infringement will be denied and Mergen's Motion for Noninfringement will be granted.

b. Claim 9

i. "A method of analysing a polynucleotide"

[14][15] Claim 9 is a method claim which reiterates many of the limitations of claim 1. (*See* Background, section II.) I have previously construed the limitations of claim 9 and, of course, rely on those constructions in this literal infringement analysis. The meaning of the preamble of Claim 9 was not ultimately disputed during claim construction, and the construction agreed upon by the parties was that, "[a] method of analysing a polynucleotide" means the process of determining information about the sequence of one or more polynucleotides whose identity is incompletely known. *See* Oxford Gene, 2004 WL 2211971, at *9. This preamble is followed by the open-ended transitional term "comprises." It is understood that "comprises," like "comprising" "is open-ended and does not exclude additional, unrecited elements or method steps." *Mars, Inc. v. H.J. Heinz Co., L.P.*, 377 F.3d 1369, 1376 (Fed.Cir.2004) (quoting MPEP, 8th ed., rev. 1 § 2111.03 (2003)); citing *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed.Cir.1997) ( "Comprising is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.").

Although I concluded that the preamble was not limiting, even if it were, Mergen practices it. Mergen uses its products for, *inter alia,* gene expression analysis. (D.I. 195, Ex. 5 at 151: 16-21, Dep. Dr. Love, Apr. 23, 2004.) To determine if a gene is expressed, one would "observe by looking at where there was hybridization, where there was not, you could determine whether-by looking at specific regions for hybridization, you could see whether a gene was expressed." (D.I. 205, Ex. E at 225, 14:52:44 6-14:52:56 10, Dr. Purdue, July 14, 2004.) According to the principles of hybridization experimentation described above (*see* Background, section II), Mergen attaches oligonucleotides of known sequence to specific regions of its array and if hybridization occurs, Mergen learns that the polynucleotide sample applied to that region of the array contains a sequence that is complementary to that of the known oligonucleotide. Thus, it is inherent in the intended use of Mergen's array that one determines information about the sequence of one or more polynucleotides whose identity is incompletely known.

ii. "applying a labelled polynucleotide to be analysed or fragments thereof"

Claim 9 continues, "applying a labelled polynucleotide to be analysed or fragments thereof." This claim term was not disputed during claim construction and was therefore, not construed. Mergen does not contest that it "applies labelled [sic] ***458** polynucleotide fragments to its

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products." (D.I. 213 at 23.) Mergen's expert, Dr. Purdue, did not discuss this claim limitation in his expert report on infringement. (D.I. 212, Ex. C at ¶ 35.) Mergen's argument is that it does not perform the same type of "analysis" on its products. (Id. at 23-24.) The type of analysis, however, is not at issue in this claim term. The focus is on the application of a labeled polynucleotide or fragments thereof. The term "to be analysed" refers to a future event, which is construed later in the claim. It is thus effectively undisputed that Mergen practices this limitation of the claim.

iii. "to an array of oligonucleotides"

"[T]o an array of oligonucleotides" was construed to mean "to two or more oligonucleotide sequences located at different regions on a single support." Oxford Gene, 2004 WL 2211971, at *4, *9-*10. OGT argues that it is clear that Mergen practices this claim limitation too (D.I. 224 at 1-3, 11) and points to Mergen's written materials which refer to its product as an "array" or "microarray." (*See* D.I. 194, Ex. 1 at 7 (Mergen's website describes its products and services as, "A Full Range of Oligo-based DNA *Microarray* Products and Services.") (emphasis added)). Mergen's argument with regard to this claim limitation is based entirely on its proposed claim construction. (D.I. 213 at 13, 24 (see Mergen's heading for what should be section IV.C.3. (although labeled as section IV.A.3.): "Whether Mergen Practices 'An Array Of Oligonucleotides' Recited in Claim 9 Depends Upon Claim Construction.")) In its discussion of claim 9, Mergen references its argument regarding this limitation as it appears in claim 1. (*Id.* at 24.) Mergen argues that its products "do not include a structured array of oligonucleotide probe sequences" that are "closely related" to other oligonucleotides in sequence. (*Id.* at 13-14.) I did not adopt Mergen's proposed construction requiring a structured array of oligonucleotides of related sequence. Oxford Gene, 2004 WL 2211971, at *4, *9-*10. Therefore, based on the construction adopted in this case, Mergen, whose arrays consist of "a plurality of independent oligonucleotide sequences" (D.I. 213 at 13-14), does practice this claim limitation.

iv. "under hybridisation conditions"

"[U]nder hybridisation conditions" was construed according to its ordinary and plain meaning to mean "under conditions suitable for hybridization." Oxford Gene, 2004 WL 2211971, at *10. Mergen's argument on this claim limitation is again based solely on its proposed claim construction, which was rejected. Mergen applies polynucleotides to the array for the purpose of hybridization to the oligonucleotides on the array. (D.I. 194, Ex. 3 at 21, Dr. Vrana's Expert Report, Ex. 4 at 10-12.) Under the construction given to this term, it is clear that Mergen practices this claim limitation because it performs its analyses under conditions suitable for hybridization.

v. "wherein the array comprises a support having an impermeable surface to which a plurality of oligonucleotides having different predetermined sequences are attached to different known regions on the surface"

The language "wherein the array comprises" is not argued by either party to have any other meaning than to introduce that the following terms describing components of the array. The following phrase, "a support having an impermeable surface," did generate controversy. I construed it to mean "a solid having a non-porous surface that does not permit diffusion through its substance." Oxford Gene, 2004 WL 2211971, at *11. Mergen's arguments***459** regarding this claim limitation, although framed as disputing whether its products have an impermeable surface, are really directed to the attachment limitation of the claim, and not the impermeable surface itself. (D.I. 186 at 13-17.) Mergen's argument seems to be that since the gel is permeable, and is on the surface of the glass slide, the gel is now the "surface" of the "support" such that the "support" in Mergen's products does not have an "impermeable surface." (*Id.* at 14.) OGT's response is that Mergen's argument "is irrelevant because it is the surface of the *glass slide* to which the oligonucleotides are attached." (D.I. 205 at 7 (emphasis in original).) OGT's argument then focuses on the attachment limitation because that limitation must be considered when determining whether the surface for Mergen's array is impermeable.

Claim 9 continues, "to which a plurality of oligonucleotides having different predetermined sequences are attached to different known regions on the surface." The key inquiry generated by this language is whether the surface of the support, to which the oligonucleotides are said to be attached, is impermeable. To answer that question, one must first decide whether the claim language requires that the oliognucleotides be directly attached to the impermeable surface or whether they can be attached to the surface via some intermediary linking agent.

That issue was resolved when I rejected Mergen's argument that "are attached" means the oligonucleotides must *themselves* be attached to the impermeable surface. (D.I. 173 at 2; *see* D.I. 209 at 17-20 (emphasis added).) The claim, by its terms, is not limited to direct attachment of the oligonucleotide itself to the impermeable surface. In fact, the invention described in the '270 patent did not attach the oligonucleotides directly to the impermeable surface. Instead, the patent describes the attachment of the oligonucleotides to a linker which is attached to the surface. (D.I. 174 at 17.) For example, the specification states:

Commercially available microscope slides (BDH Super Premium 76x26x1 mm) were used as supports. These were derivatised with a long aliphatic linker that can withstand conditions used for the deprotection of the aromatic heterocyclic bases, i.e. 30% NH3 at 55 for 10 hours. The *linker,* bearing a hydroxyl group which *serves as a starting point for the subsequent oligonucleotide,* is synthesised in two steps.

('270 patent, col. 8, ll. 59-65 (emphasis added).)

Mergen argues that when it constructs its array, it attaches oligonucletodies to a *permeable* surface of a support, not to an *impermeable* surface of a support as required by claim 9. (D.I. 186 at 13-17 (emphasis added).) OGT counters that Mergen's accused products are attached to an impermeable surface of a support through a coating of polyacrylamide, and therefore satisfy this claim limitation. (D.I. 180 at 7-9.)

Mergen's product consists of a glass slide with a polyacrylamide matrix attached. (*See* D.I. 187, Exs. D, E, F.) There is no dispute that the glass slide itself has an impermeable surface. *Id.* The oligonucleotides are attached to the polyacrylamide matrix which is attached to the surface of the glass slide. Thus, the oligonucleotides are attached to the surface of the glass slide via the polyacrylamide matrix. *Id.* The polyacrylamide matrix on Mergen's glass slides functions as a linker between the oliognucloetides and the impermeable surface of the glass slide support. Therefore, the polyacrylamide matrix performs the same function as the linker described in the specification, namely***460** attachment of the oligonucleotides to the impermeable surface of a support.

The other claim term limitations, "a plurality of oligonucleotides having different predetermined sequences are attached to different known regions on the surface" are also practiced by Mergen. First, the oligonucleotides sequences are known. (*See* D.I. 194, Ex. 3 at 18, Dr. Vrana's Expert Report, Ex. 4 at 1-2.)[FN12] Second, the oligonucleotides are attached to different known regions on the surface of the support. "The design of the oligonucleotide sequences follows a set of rigorously controlled criteria, including unique match with GenBank's human database, minimal variation ... and consistent position within the gene sequences ...." (Mergen's ExpressChip Instruction Manual at 2, 18-19 in D.I. 194, Ex. 3, Dr. Vrana's Expert Report, Ex. 4 (describing the "Microarray Coordinate System" whereby Mergen or its customers can determine which gene is expressed based on the known location of each oligonucleotide sequence attached to the support).) Therefore, it is also clear that Mergen practices these limitations of claim 9.

FN12. Mergen's customers can determine which genes are expressed in the polynucleotide sample by knowing which oligonucleotides are attached to the array. (*See* D.I. 194, Ex. 3, Dr. Vrana's Expert Report, Ex. 4 at 1.) Mergen's ExpressChip Instruction Manual directs its customers to its website where it provides "[g]ene information on each arrayed spot and links to NCBI's GenBank/UniGene databases ...."(*Id.*)

vi. "analysing the polynucleotide"

The term "analysing the polynucleotide" uses the same language discussed in the preamble of claim 9 above. (*See* Discussion, section IV.B.1.b.i.) Consistent with that interpretation, "analysing the polynucleotide," therefore means the process of determining information about the sequence of one or more polynucleotides whose identity is incompletely known. *Oxford Gene,* 2004 WL 2211971, at *11. Mergen's argument regarding this claim limitation is focused on what is being accomplished by the analysis, as opposed to whether an analysis occurs. For example, Mergen argues that its products "do not provide sequence information about polynucleotides." (D.I. 213 at 30.) Mergen's analysis, however, does indeed involve "determining information about the sequence of one or more polynucleotides whose identity is incompletely known" because Mergen admits, "[t]he information obtained using the Mergen slide is limited to gaining an indication of the presence of a sequence [of a polynucleotide] with some degree of similarity ... [to] an oligonucleotide on the slide." (D.I. 186 at 20.) In short, Mergen practices this claim limitation because some

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information about the sequence of the unknown polynucleotides is determined through its analysis.

vii. "by observing the regions where the polynucleotide or fragement thereof hybridizes and the regions where the polynucleotide or fragment thereof does not hybridize"

I previously construed "by observing the regions where the polynucleotide or fragement thereof hybridizes and the regions where the polynucleotide or fragment thereof does not hybridize" according to its plain and ordinary meaning, to mean exactly what it says. Oxford Gene, 2004 WL 2211971, at *11. Mergen argues that it does not practice this claim limitation because "Mergen seeks to analyze the polynucleotides ... not by observing the regions to which each polynucleotide (or fragments thereof) hybridize or do not hybridize (since this is already known), but rather by determining whether hybridization is seen at specific, previously established***461** location [sic]." (D.I. 213 at 30.) OGT argues that Mergen practices this claim limitation because "Mergen visualizes the results of hybridization, so that one can see where hybridization occurred and where it did not based on the presence or absence of [a] signal at the various spots on an array." (D.I. 180 at 14.)

It is clear that Mergen's arrays are analyzed by observing the regions where the polynucleotide or fragment thereof hybridized and the regions where it did not. Experiments run on Mergen's arrays produce regions with hybridization and regions without hybridization. Mergen and its customers visualize the results of the hybridization and in so doing, they see where hybridization has occurred and where it has not, based on the presence or absence of a signal at the various spots on an array. (*See* D.I. 194, Ex. 3, Dr. Vrana's Expert Report, Ex. 4, Mergen's ExpressChip Instruction Manual at 18.) As Mergen's instruction manual states, "identification of a positive signal is directly dependent upon the abundance of a specific mRNA.... [T]he vast majority of genes are not highly expressed and signal intensities can vary greatly." (*Id.*) It is only by detecting whether a particular region produces a signal, that Mergen can make a determination regarding whether a particular gene is expressed. This process inherently involves observing the regions where the polynucleotide or fragment thereof hybridizes and the regions where it does not. Mergen states that "[t]he information obtained using the Mergen slide is limited to gaining an indication of the presence of a sequence [of a polynucleotide] with some degree of similarity ... [to] an oligonucleotide on the slide." (D.I. 186 at 20.) Again, by Mergen's own admission, once the presence of the polynucleotide is determined, some information about its sequence is learned. The fact that this information is gained regarding the polynucleotide's sequence is enough to warrant the conclusion that Mergen practices this final limitation of claim 9.

Based on the foregoing analysis of the limitations in claim 9 and the evidence of record, I conclude that Mergen practices each and every limitation of that claim of the '270 patent and therefore literally infringes. Mergen has not raised a genuine issue of material fact such that summary judgment for OGT is inappropriate. Therefore, OGT's Motion for Infringement will be granted as to claim 9 (D.I. 179) and Mergen's Motion for Noninfringement as to this claim will be denied (D.I. 185).

c. Claim 10

[16] Claim 10 is also a method claim which reiterates many of the limitations of claims 1 and 9. (*See* Background, section II.) I previously held that the preamble, "[a] method of comparing polynucleotide sequences" was not limiting, Oxford Gene, 2004 WL 2211971, at *12, and Mergen's arguments to the contrary are not persuasive.

Even if the preamble were limiting, however, Mergen performs "the process of determining relative information about two or more polynucleotide sequences." *See id.*(noting the construction for the preamble of claim 10, were it to be limiting). Mergen uses its products for, *inter alia,* gene expression analysis. (D.I. 195, Ex. 5 at 151: 16-21, Dep. Dr. Love, Apr. 23, 2004.) According to the principles of hybridization experimentation (*see* Background, section II), Mergen attaches oligonucleotides of known sequence to specific regions of its microarrays and, if hybridization occurs, Mergen learns that the polynucleotide sample applied to that region of the array contains a sequence that is complementary to that of the known oligonucleotide probe. Thus, when more than one ***462** polynucleotide sequence is present in a sample, it is inherent in the intended use of Mergen's microarray that the user will determine relative information about the sequences of those polynucleotides whose complement is represented by an oligonucleotide probe. Therefore, as with claim 9, even if the preamble were limiting, Mergen's microarrays are used to practice this limitation.

Nearly all of the limitations of claim 10 are present in claim 9. *See* Oxford Gene, 2004 WL 2211971, at *12. Since I have determined that Mergen literally infringes

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claim 9 of the '270 patent, it is only necessary to consider the single limitation of claim 10 that differs from claim 9.FN13 The last limitation of claim 10, "observing the differences between the patterns of hybridisation," is not present in claim 9. I previously construed "observing the differences between the patterns of hybridisation" to mean exactly what it says. *Oxford Gene*, 2004 WL 2211971, at *12-*13.

FN13. The limitations that are present in both claim 9 and 10, include: (1) "applying the polynucleotides to an array of oligonucleotides," (2) "under hybridizing conditions," (3) "wherein the oligonucleotides have different predetermined sequences and are attached at different known locations," and (4) "on an impermeable surface of a support." *See Oxford Gene*, 2004 WL 2211971, at *12.

OGT argues that Mergen directly practices this claim limitation and hence infringes claim 10. (D.I. 180 at 17-18.) For support, OGT points to three acts by Mergen which OGT alleges are infringing. First, Mergen "compares the hybridization of the target sample sequences to the spots on the array known to serve as "positive controls" in order to determine the difference in intensity between hybridization at various spots on the array." (D.I. 180 at 17.) Second, Mergen practices this claim limitation when it "observe[s] the differences between hybridization expression patterns on two distinct arrays"(*id.*) as it compares the hybridization results of a normal sample to that of a disease sample. (D.I. 195, Ex. 16, Dep. Dr. Hu at 104-05, July 8, 2004.) Third, Mergen offers a "pairwise analysis," such that "Mergen and its customers can visualize side-by-side differences between the patterns of hybridization on two distinct arrays." (D.I. 180 at 18; D.I. 195, Ex. 5, Dep. Dr. Love at 75-76, Apr. 23, 2004.) Mergen counter-argues that "the only reasonable interpretation of the 'observing patterns of hybridization' term to one skilled in the art, would be the spatial distribution over the microarray of regions to which the polynucleotide hybridized and regions to which the polynucleotide did not hybridize." (D.I. 213 at 33 (citing Ex. C, Dec. Dr. Purdue).)

That argument is essentially a claim construction argument which Mergen did not advance during claim construction. The assertion is that the "observing patterns of hybridization" limitation of claim 10 can only be understood to mean that the analysis is practiced on a single array. The sole support offered for that assertion is a "see" citation to the declaration of Mergen's expert, Dr. Purdue. (D.I. 213 at 33.) In his Declaration, Dr. Purdue does state a conclusion as to the meaning of "patterns of hybridization" to one of skill in the art (D.I. 215, Ex. C at ¶ 18, Dec. Dr. Purdue), but he does so without without citing any basis for that conclusion. Thus, this entirely new definition of "pattern," never before articulated in any brief or proposed claim construction, is unsupported by any evidence but the bare assertion of Mergen's expert. I reject Mergen's belated attempt to shape claim construction and I decline to add further restrictions to the interpretation of claim 10.

***463** At least two of Mergen's activities directly infringe claim 10. First, Mergen "observe[s] the differences between hybridization expression patterns on two distinct arrays" (D.I. 180 at 17) as it compares the hybridization results of a normal sample to that of a disease sample. (D.I. 195, Ex. 16, Dep. Dr. Hu at 104-05, July 8, 2004.) Second, Mergen offers a "pairwise analysis," such that "Mergen and its customers can visualize side-by-side differences between the patterns of hybridization on two distinct arrays." (D.I. 180 at 18; D.I. 195, Ex. 5, Dep. Dr. Love at 75-76, Apr. 23, 2004.) Furthermore, Mergen's ExpressChip Protocol Synopsis and ExpressChip Instruction Manual refer to a comparison of hybridization patterns: "[t]he sample's expression *pattern* is usually compared with that of a control sample for differential analysis." (D.I. 194, Ex. 3, Dr. Vrana's Expert Report, Ex. 9, Mergen's ExpressChip Protocol Synopsis, at 1 (emphasis added); D.I. 194, Ex. 3 at 18, Dr. Vrana's Expert Report, Ex. 4, Mergen's ExpressChip Instruction Manual, at 1 (emphasis added).)

In light of those activities and Mergen's failure to respond to the arguments raised by OGT,FN14 I hold that Mergen literally infringes claim 10 because it practices each and every limitation of claim 10 of the '270 patent, as discussed here and in the corresponding discussion involving the claim terms that are also limitations in claim 9. Mergen has not raised any genuine issue of material fact such that summary judgment for OGT is inappropriate. Therefore, with respect to claim 10, OGT's Motion for Infringement (D.I. 179) will be granted and Mergen's Motion for Noninfringement (D.I. 185) will be denied.

FN14. Mergen's response to the arguments raised by OGT is entirely based on its own claim construction and claim limitations not adopted by this court. (*Compare* D.I. 213 at 31-33, *with Oxford Gene*, 2004 WL 2211971 at *12-*13.)

Aside from arguing its claim construction, Mergen has not provided any basis for concluding that these specific activities do not infringe. (*See* D.I. 213 at 31-33.)

2. Indirect Infringement

[17] OGT has moved for summary judgment that Mergen indirectly infringes claims 9 and 10. (D.I. 180 at 1.) Whether directly infringing or not, "a party may still be liable for inducement or contributory infringement of a method claim under 35 U.S.C. §§ 271(b), (c) if it sells infringing devices to customers who use them in a way that directly infringes the method claim." *Linear Tech. Corp. v. Impala Linear Corp.*, 379 F.3d 1311, 1326 (Fed.Cir.2004) (citing *RF Del., Inc. v. Pac. Keystone Techs., Inc.*, 326 F.3d 1255, 1267 (Fed.Cir.2003)).

a. Inducing Infringement

[18][19] Pursuant to 35 U.S.C. § 271(b), "[w]hoever actively induces infringement of a patent shall be liable as an infringer." Direct infringement is a prerequisite to liability for inducing infringement. *Met-Coil Sys. Corp. v. Korners Unlimited, Inc.*, 803 F.2d 684, 687 (Fed.Cir.1986). Additionally, the alleged infringer must have knowingly induced infringement. *Manville Sales Corp. v. Paramount Sys., Inc.*, 917 F.2d 544, 553 (Fed.Cir.1990) (citing *Water Techs. Corp. v. Calco, Ltd.*, 850 F.2d 660, 668 (Fed.Cir.1988)). "Although section 271(b) does not use the word 'knowing,' the case law and legislative history uniformly assert such a requirement." *Water Techs.*, 850 F.2d at 668 (internal citations omitted). Liability can be established by proving that the party accused of inducement "should have known that its actions would induce actual infringement." *See* *464*Mentor H/S, Inc. v. Medical Device Alliance, Inc.*, 244 F.3d 1365, 1379 (Fed.Cir.2001) (citing *Manville Sales Corp. v. Paramount Sys.*, 917 F.2d 544, 553 (Fed.Cir.1990)). A patentee may prove intent through circumstantial evidence. *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1365 (Fed.Cir.2004) (citing *Water Techs.*, 850 F.2d at 668 (noting that "circumstantial evidence may suffice" in proving intent)).

[20] With respect to inducing infringement under 35 U.S.C. § 271(b), I conclude that OGT has met its burden of showing that Mergen's actions induced infringing acts by its customers and that Mergen knew or should have known that its actions would induce actual infringement. In particular, OGT has argued that the following circumstantial evidence establishes Mergen's active inducement of infringement of claims 9 and 10:(1) Mergen designs its microarray kits for a particular use (*see* D.I. 180 at 11; D.I. 195, Ex. 8 at 69-70, Dep. Dr. Love, June 15, 2004); (2) Mergen sells its products as kits, which include all of the necessary components to the perform the directly infringing acts: "a pair of pre-arrayed slides, materials, and reagents sufficient for the processing of two slides" (*see* D.I. 195, Ex. 4 at 2, ExpressChip Instruction Manual); (3) Mergen instructs its customers on how to use its microarray kits in a manner which has been found to be infringing (*see* D.I. 195, Ex. 4, ExpressChip Instruction Manual; Ex. 6, Protocol Synopsis; Ex. 8 at 52-53, Dep. Dr. Love, June 15, 2004); and (4) Mergen's customers follow those instructions and use the microarrays in the same manner as Mergen, which was found, *see supra,* to be directly infringing (*see* D.I. 180 at 11; D.I. 195, Ex. 5 at 64, Dep. Dr. Love, Apr. 23, 2004, Ex. 8 at 70, 107, 161, Dep. Dr. Love, June 15, 2004). Mergen has not disputed the evidence described above, nor argued why a finding of summary judgment of active inducement is unwarranted. Mergen's only response to OGT's arguments is that, "[s]ince there is no direct infringement of claims 9 (and 10, as set forth in this opposition), there is no indirect infringement." (D.I. 213 at 22 (citation omitted).)

Based on the evidence of Mergen's active inducement of claims 9 and 10, as alleged by OGT, and the lack of any rebuttal evidence by Mergen, I find that Mergen actively induced its customers to infringe claims 9 and 10 of the '270 patent. Notably, evidence of sales and instruction manuals supports a finding of induced infringement. *See, e.g., Water Techs.*, 850 F.2d at 668 (affirming inducement finding based on circumstantial evidence including helping customers and providing instructions); *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 1272 (Fed.Cir.1986) (affirming finding of inducement based on circumstantial evidence such as extensive sales and instruction manual). It is clear that Mergen sold its microarray kit, encouraged its customers to follow the instruction manual describing the intended method of use, and that its customers did so use it, resulting in the direct infringement of claims 9 and 10. Therefore, I will grant OGT's Motion for Infringement based on Mergen's active inducement of its customers' direct infringement of claims 9 and 10 of the '270 patent.

b. Contributory Infringement

[21] The doctrine of contributory infringement is codified

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at 35 U.S.C. § 271(c):

Whoever offers to sell or sells within the United States or imports into the United States a component of a patented machine, manufacture, combination or composition, or a material or apparatus for use in practicing a patented process, constituting a material part of the invention,***465** knowing the same to be especially made or especially adapted for use in an infringement of such patent, and not a staple article or commodity of commerce suitable for substantial noninfringing use, shall be liable as a contributory infringer.

This form of infringement is premised on the idea that a defendant who displays sufficient culpability should be held liable as an infringer, even though he may not have made, used, or sold a patented invention. *Hewlett-Packard Co. v. Bausch & Lomb Inc.,* 909 F.2d 1464, 1469 (Fed.Cir.1990). "Such liability was under a theory of joint tortfeasance, wherein one who intentionally caused, or aided and abetted, the commission of a tort by another was jointly and severally liable with the primary tortfeasor." *Id.* (internal citation omitted).

[22] To prove contributory infringement, a plaintiff must demonstrate the following: (1) an offer to sell, sale, or import; (2) a component or material for use in a patented process constituting a material part of the invention; (3) knowledge by the defendant that the component is especially made or especially adapted for use in an infringement of such patent; and (4) the component is not a staple or article suitable for substantial noninfringing use. *Union Carbide Chems. & Plastics Tech. Corp. v. Shell Oil Co.,* No. Civ. 99-CV-274-SLR, Civ. 99-846-SLR, 2004 WL 1305849, *7 (D.Del. June 9, 2004) (citing 35 U.S.C. § 271(c)). Further, contributory infringement also requires proof of actual direct infringement by a customer of the defendant. *See Novartis Pharms. Corp. v. Eon Labs Mfg., Inc.,* 363 F.3d 1306, 1308 (Fed.Cir.2004) (internal citations omitted). However, if use of the component by the defendant's customers necessarily infringes the patent, actual proof of an instance of direct infringement is not required. *Dynacore Holdings Corp. v. U.S. Philips Corp.,* 363 F.3d 1263, 1275-76 (Fed.Cir.2004). "[A] seller of a 'material part' of a patented item may be a contributory infringer if he makes a non-staple article that he knows was 'especially made or especially adapted for use in an infringement of such patent.' " *Husky Injection Molding Sys. Ltd. v. R & D Tool & Eng'g Co.,* 291 F.3d 780, 784 (Fed.Cir.2002) (quoting 35 U.S.C. § 271(c); *Dawson Chem. Co. v. Rohm & Haas Co.,* 448 U.S. 176, 219, 100 S.Ct. 2601, 65 L.Ed.2d 696 (1980)). Section 271(c) has been interpreted to require not only knowledge that the component was especially made or adapted for a particular use but also knowledge of the patent which proscribed that use. *See Hewlett-Packard,* 909 F.2d at 1469 n. 4 (*citing Aro Mfg. Co. v. Convertible Top Replacement Co.,* 377 U.S. 476, 488, 84 S.Ct. 1526, 12 L.Ed.2d 457 (holding that section 271(c) does require a showing that the alleged contributory infringer knew that the combination for which his component was especially designed was both patented and infringing.))

[23] OGT alleges that Mergen is liable for contributory infringement because it contributes to the directly infringing acts of its customers. (D.I. 180 at 11.) Mergen's only response is the same as it was with respect to inducing infringement: "[s]ince there is no direct infringement of claims 9 (and 10, as set forth in this opposition), there is no indirect infringement." (D.I. 213 at 22 (citation omitted).) Because I have found that by following the instructions provided by Mergen, its customers directly infringe claims 9 and 10 (*see supra* section VI.B.2.a.) the question becomes whether OGT has presented sufficient evidence to establish that Mergen contributed to its customers infringement.

First, OGT alleges that Mergen offers to sell and does sell microarray kits, and that ***466** Mergen's customers use those microarray kits in a manner that infringes claims 9 and 10 of the '270 patent. (D.I. 180 at 11, 17.) Second, the microarray component is a material part of the invention because it is the support upon which the claimed methods of use are performed. (*See id.*) Third, Mergen knew that the microarray kits were made for a particular use and that such use may be proscribed by the '270 patent. (*See* E-mail from Loretta Tse, Ph.D., Director, Business Development, Mergen, to Drs. Miller and Shelley (Aug. 10, 2000) (inquiring about a license in the area of DNA microarray technology and noting that Mergen's research has indicated that the '270 patent is relevant to Mergen's "manufacturing and marketing plan"); Instruction Manual, D.I. 195, Ex. 4.) The record shows that by August 10, 2000, Mergen was aware of the '270 patent and that its activities might infringe some of the claims. Finally, OGT has alleged that there is "no substantial non-infringing use of the oligonucleotide arrays except to use them in ... [an infringing] way ...." (D.I. 180 at 11; D.I. 195, Ex. 3 at 23, Dr. Vrana's Expert Report.) Mergen has provided no argument, besides the one sentence quoted above.

Based on the uncontroverted evidence of contributory

infringement, Mergen is liable for contributory infringement as "[a] seller of a 'material part' of a patented item ... [who] makes a non-staple article that he knows was 'especially made or especially adapted for use in an infringement of such patent.' " *Husky Injection Molding,* 291 F.3d at 784 (quoting 35 U.S.C. § 271(c); *Dawson Chem. Co. v. Rohm & Haas Co.,* 448 U.S. 176, 219, 100 S.Ct. 2601, 65 L.Ed.2d 696 (1980)). Therefore, OGT's Motion for Infringement will be granted with respect to Mergen's contributory infringement.

**V. CONCLUSION**

For the foregoing reasons, Accordingly, OGT's Motion for Validity (D.I. 177) will be DENIED; its Motion for Infringement (D.I. 179) will be GRANTED in part, as it relates to direct and indirect literal infringement of claims 9 and 10, and DENIED in part, as it relates to claim 1; and its Motion to Strike (D.I. 202) will be DENIED as moot. Mergen's Motion for Invalidity (D.I. 181) will be DENIED; its Motion for Non-Infringement (D.I. 185) will be GRANTED in part, with respect to claim 1, and DENIED in part, with respect to claims 9 and 10; and its Motion for Invalidity of Claim 1 (D.I. 190) will be DENIED without prejudice.

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## X. RELATED PROCEEDINGS APPENDIX

(5) Order on Motion for Reconsideration, Oxford Gene Technology Ltd. v. Mergen Ltd., et al., Civil Action No. 02-1695-KAJ before the United States District Court for the District of Delaware, 2005 WL 121797, January 7, 2005.

H Oxford Gene Technology Limited v. Mergen Ltd.
D.Del.,2005.
Only the Westlaw citation is currently available.
United States District Court,D. Delaware.
OXFORD GENE TECHNOLOGY LIMITED, Plaintiff,
v.
MERGEN LTD., et al., Defendants.
**No. Civ.A. 02-1695-KAJ.**

Jan. 7, 2005.

*ORDER*

JORDAN, J.
***1** Presently before me is a motion (D.I. 262; the "Motion") filed by Mergen Limited ("Mergen") seeking reconsideration of my November 19, 2004 Order granting Oxford Gene Technology Limited's ("OGT") Motion for Partial Summary Judgment of Infringement (D.I.179). At the pre-trial conference on January 4, 2005, I denied Mergen's Motion on all but one issue, and reserved ruling on that issue until after further consideration of the arguments presented in the parties' briefing and during the pre-trial conference. The only remaining issue from Mergen's Motion is whether Mergen practices all of the elements of claim 10 of the '270 patent, including the last element, "observing the differences between the patterns of hybridisation."('270 patent, col. 16, ll. 64-65.) Mergen admits that, under the court's claim construction ruling, it does practice all of the elements of claim 10 with regard to some of its products (Transcript at 17:11-19, Pre-Trial Conf., Jan. 4, 2005; D.I. 262 at 7), but it also argues that it does not and cannot do so with the majority of its product line because it performs its analyses using *two* distinct supports rather than using a single support, as required by the claim construction ruling. (D.I. 262 at 6-7.) For the reasons that follow, I deny Mergen's Motion.

In its Motion, Mergen argues that it does not infringe claim 10 when it uses two supports in its analyses because, in order to infringe, all of the elements of claim 10 must be performed on a single support. (*See* D.I. 262 at 7.) Mergen asserts that the "vast majority of the time ... [it] use[s] two distinct arrays located on two supports" and therefore does not practice each and every element of claim 10. (D.I. 262 at 7.) Mergen bases this argument on my construction of the claim term "an array of oligonucleotides," which I said means "two or more oligonucleotide sequences located at different regions on a *single* support."(*Id.* at 6-7 (emphasis added in original).) Essentially, Mergen's argument is that "about 90 percent" of the time, it uses two supports in its analyses, and in so doing, it does not practice the last limitation of claim 10, namely "observing the differences between the patterns of hybridisation," on any one support, but rather that it observes "the differences between the patterns of hybridisation" across two supports. (*Id.;* Transcript at 17:16, Pre-Trial Conf., Jan. 4, 2005.)

In the Memorandum Opinion and Order dated November 19, 2004, I concluded, *inter alia,* that Mergen practices each and every limitation of claim 10 and granted summary judgment for OGT on the issue of literal infringement. (D.I. 245 at 32-33.) That ruling was based on my Memorandum Opinion and Order on September 29, 2004 (D.I. 237; D.I. 238), in which, as earlier noted, I construed "an array of oligonucleotides" to mean "two or more oligonucleotide sequences located at different regions on a *single* support."(D .I. 237 at 2; D.I. 238 at 27 (emphasis added).) OGT's proposed claim construction was nearly identical to the construction I gave the claim language. OGT had proposed the following construction: "a set of two or more oligonucleotide sequences located at different regions on a *single* support."(D.I. 174 at 20; D.I. 173 at 3 (emphasis added).) Nonetheless, in its Opposition to Mergen's Motion, OGT argues that "there is no restriction in claim 10 against using more than one such 'array" ' and cited *Altiris, Inc. v. Symatec Corp.,* 218 F.3d 1363, 1373-74 (Fed.Cir.2003) for the proposition that the article "an" in patent claims means "one or more." (D.I. 263 at 10.)

***2** There is no dispute that in open-ended claims, such as claim 10, "a" or "an" generally means "one or more." *Altiris,* 218 F.3d at 1373 (citing KCJ Corp. v. Kinetic Concepts, Inc., 223 F.3d 1351, 1356 (Fed.Cir.2000)). However, the Federal Circuit's claim construction rulings in cases standing for that proposition were based on a finding that the patentee did not evince a clear intent to limit the article to mean

(5)

"one and only one." *See* KCJ, 223 F.3d at 1356;*see Altiris,* 218 F.3d at 1373. Here, that is not the case. OGT expressly requested and advocated the claim construction limiting the method of claim 10 to the observation of differences between hybridization patterns on a "single" support. (D.I. 174 at 20; D.I. 173 at 3.) At the pre-trial conference, I specifically asked counsel for OGT whether they were arguing for a different claim construction than that which they had originally sought, and counsel responded they were not. (Transcript at 19:25-20:2, Pre-Trial Conf., Jan. 4, 2005.) Instead, OGT's argument was that "there is no requirement in the comparison aspect that requires the comparison to be made within or among locations on that same support."(*Id.* at 19:1-3.)

Claim 10 states in its entirety:

A method of comparing polynucleotide sequences, which method comprises:

applying the polynucleotides to an array of oligonucleotides under hybridizing conditions, wherein the oligonucleotides have different predetermined sequences and are attached at different known locations on an impermeable surface of a support, and

observing the differences between the patterns of hybridisation.

('270 patent, col. 16, ll. 57-65.) Because the differences referred to in the last step of the claim are to be found within "an array of oligonucleotides," and because "an array of oligonucleotides" means "two or more oligonucleotide sequences located at different regions on a *single* support" (D.I. 237 at 2; D.I. 238 at 27 (emphasis added)), literal infringement will occur only when all of the elements of the method in claim 10 are performed on a single support.

The question then becomes whether Mergen practices the last element of claim 10 even when it uses two distinct supports in its analyses. In other words, is it the case that, even when using two supports (e.g., microscope slides) to conduct an analysis because one is interested in the differences between two separate arrays, one nevertheless also looks for differences that exist on each of the arrays? If that is the case, then there is still literal infringement, regardless of whether one takes the further step of observing differences between the arrays on the separate supports. If Mergen observes "the differences between the patterns of hybridisation" on one support then it practices all of the elements of claim 10 and literally infringes. If, on the other hand, Mergen observes "the differences between the patterns of hybridisation"*only* by comparing the results of two distinct supports and it makes no observation of hybridization differences on any one support, then it does not practice this limitation as I have construed it, and therefore does not literally infringe claim 10.

*3 This same issue was raised by OGT during the summary judgment briefing. OGT asserted that the record is undisputed in showing that, even in undertaking an analysis using two slides, Mergen practices all of the limitations of claim 10 on each individual slide because, at a minimum, they observe differences in the pattern of hybridization on a single slide by seeing the difference between a control spot on each slide and the rest of the spots on the slide.[FN1](D.I. 180 at 17-18.) Mergen did not address that specific argument or advance evidence in response to it to raise a genuine issue of material fact. OGT's evidence and argument in this regard are persuasive and dispositive of this issue.

FN1. Even if one were to assume that every spot on a single slide was indistinguishable from every other spot except the control, there would still be a difference "between the patterns of hybridisation" ('270 patent, col. 16, ll. 64-65) on the slide in the sense that the control would stand out distinctly from the rest of the spots.

Accordingly, IT IS HEREBY ORDERED that Mergen's Motion for Reconsideration (D.I.262) is DENIED.[FN2]

FN2. At this juncture, the foregoing discussion may be academic because the practical effect of my previous ruling that Mergen infringes claim 9 of the '270 patent may well be that Mergen will be liable for damages with respect to all of its products, if the claim is not proven invalid.

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